THE American Journal OF Gastroenterology

VOL. 29, NO. 1 JANUARY, 1958

Clinical Evaluation of Paper Electrophoresis

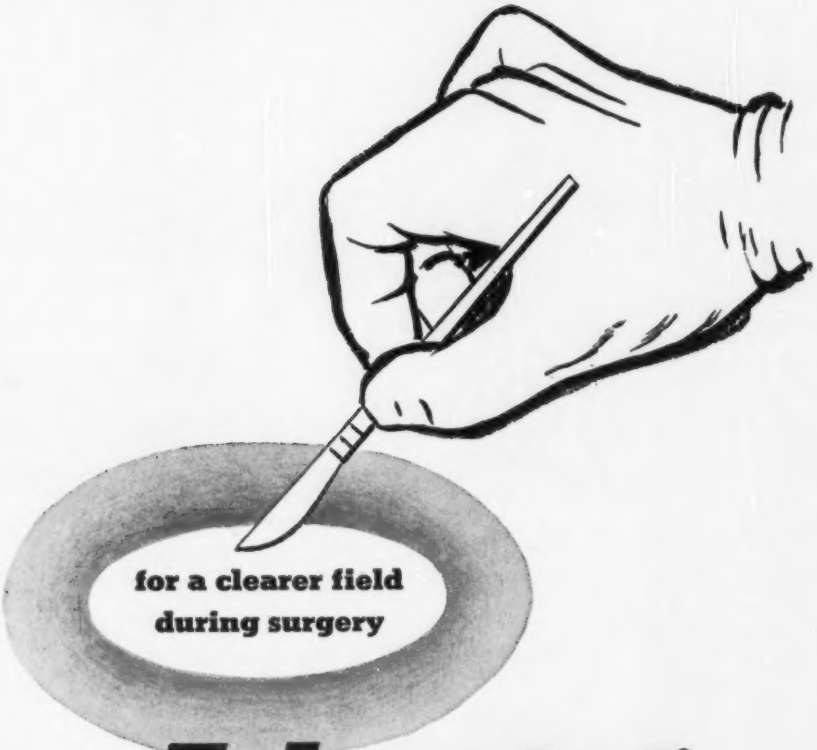
Pneumoperitoneum After Gastroscopy

Polycystic Disease of the Liver

Effect of Anti-Inflammatory Hormones Upon the Pancreatitis Produced by Stylomycin Aminonucleoside

Twenty-third Annual Convention
New Orleans, Louisiana
19, 20, 21, 22 October 1958

Official Publication
AMERICAN COLLEGE
OF GASTROENTEROLOGY



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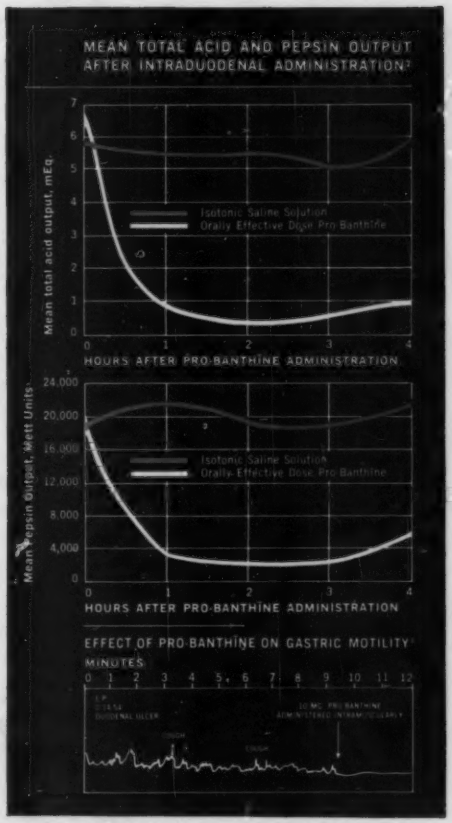
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1. Barowsky, H., in discussion of Barowsky, H.; Schwartz, S. A., and Lister, J.: Experience with Short-Term Intensive Anticholinergic Therapy of Peptic Ulcer, Am. J. Gastroenterol. *27*:156 (Feb.) 1957.
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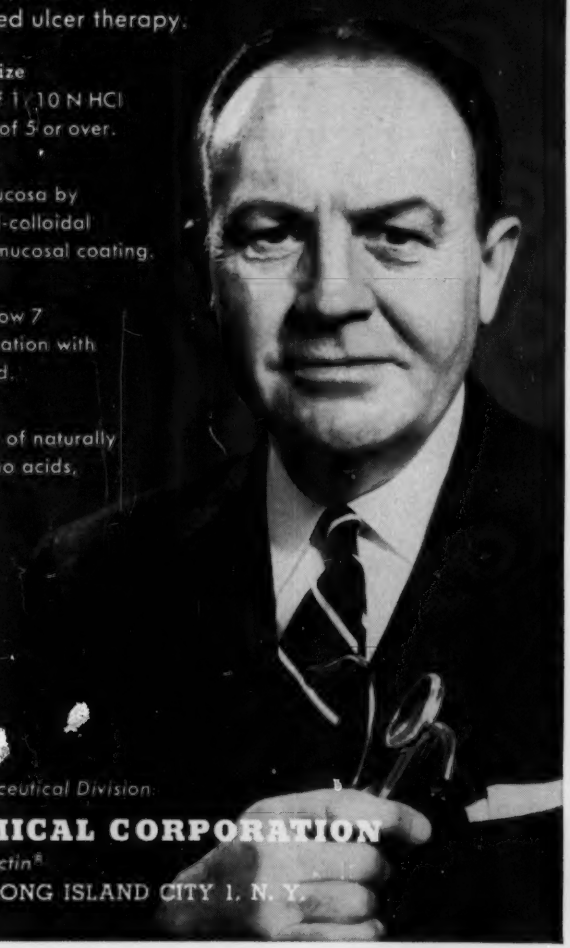

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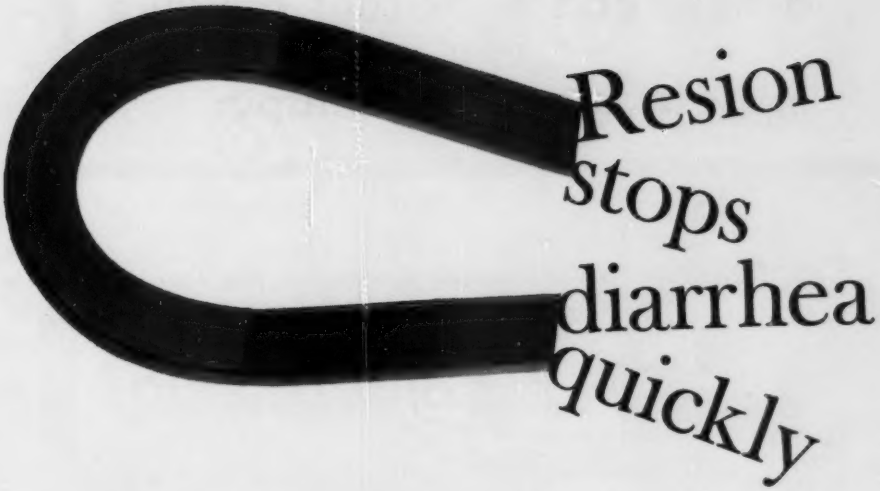

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2. Cayer, D.; Sohmer, M.F., and Sugg, W.C.: North Carolina M.J. *18*:311 (Aug.) 1957.
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6. Boyd, E.M.: Canad. M.A.J. *76*:286 (Feb. 15) 1957.

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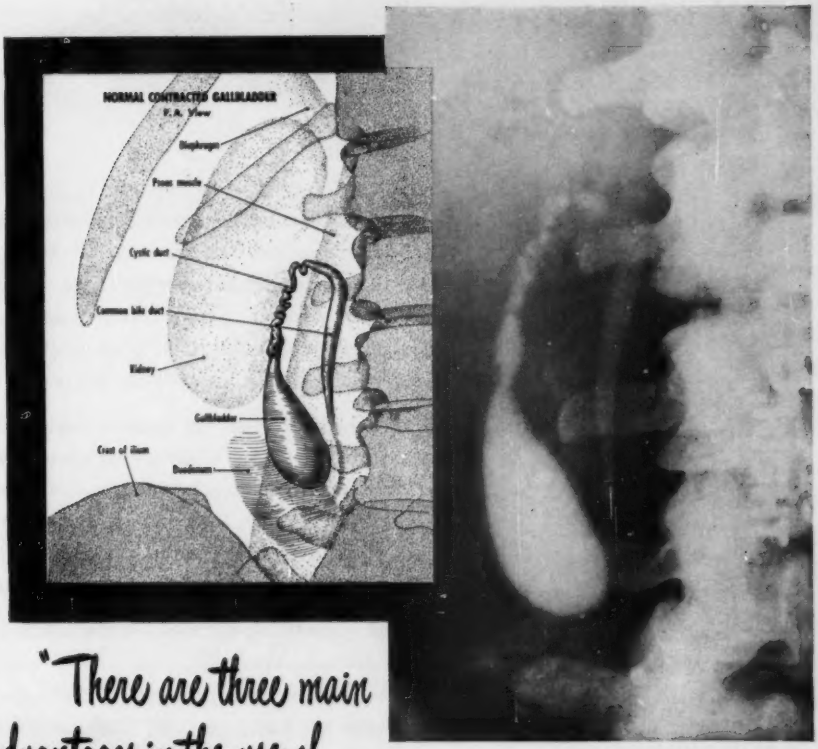

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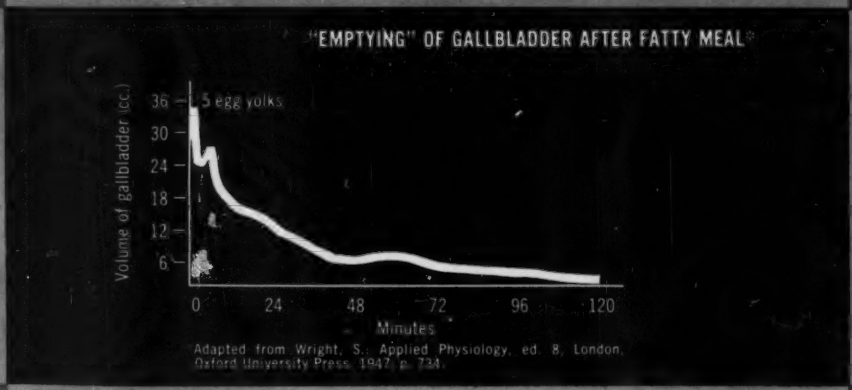

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Source—Lichtman, S. S.: Diseases of the Liver, Gallbladder and Bile Ducts, ed. 3, Philadelphia, Lea & Febiger, 1953, vol. 2, p. 1177.

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VOLUME 29 JANUARY, 1958 NUMBER 1

CLINICAL EVALUATION OF PAPER ELECTROPHORESIS

III. CORRELATION BETWEEN THE PLASMA ANTITHROMBIN TITER LEVELS AND THE ELECTROPHORETIC SERUM PROTEIN PATTERNS IN PATIENTS WITH LIVER DISEASE

A. ALLEN GOLDBLOOM, M.D., F.A.C.G.
IRVING INNERFIELD, M.D.
MARCUS A. FEINSTEIN, M.D.
NICHOLAS BRITTIS, M.D.
and
FERNANDO GARIP, M.D.
New York, N. Y.

The liver is the master organ in the body and is concerned with the regulation and preservation of all the complex chemical and physical relationships of the physiology of life. Since the functions of the liver are many and varied, it is impossible to discuss all of them. Indeed, a recent survey of the literature enumerated 97 listed liver function tests[1].

The authors will confine themselves to an abnormal liver function test involving the major enzyme system whose antithrombin titer specifically parallels variations in the severity and extent of liver cell damage. The level of the antithrombin titer activity and paper electrophoretic patterns were performed simultaneously for effective comparison of the severity and extent of liver cell damage[2].

Blood chemical determinations may not corroborate underlying pathological liver changes[3], nor yield information concerning the changes in various protein fractions of the serum or plasma[4,5]. Recent electrophoretic technics permit the clinician the possibility of detecting blood protein changes in a simple and inexpensive manner[6-9].

From the New York Medical College-Metropolitan Medical Center (Metropolitan Hospital Division) New York, N. Y.
Aided by a grant from the Sophie D. Cohen and William W. Cohen Foundation.

Material and Methods

Hospitalized male patients ranging in age from 16 to 91 years (average 57 years) were studied from an acute, active general medical service. Patients with a history and examination suggestive of some hepatic disturbance were chosen. The object was to further evaluate clinically two laboratory procedures, namely: paper electrophoresis of the patient's serum protein; the plasma antithrombin titer as a liver function test; and any correlations between the two procedures to explain the mechanism for the varied antithrombin titer levels.

Technic of Blood Collection

Fasting nonoxalated blood, 30-40 c.c., was obtained and the serum was utilized. Twenty ml. of the fasting blood were carefully poured into a dry conical

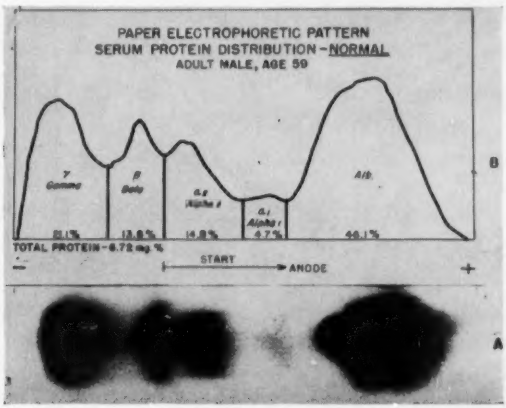


Fig. 1—Comparison of dyed filter paper electrophoretic pattern (A), and corresponding densitometered and planimetered pattern (B) of serum proteins in a *normal adult male,* age 59. The A/G Ratio from the percentage components is 0.85. The total protein 6.72 mg. per cent and A/G Ratio 1.7:1 (Chemical determination).

nongraduated centrifuge tube, containing no coagulant. These tubes were closed with special parafilm and not corked to prevent contacts of foreign substances with the blood. For the plasma antithrombin titer liver test, 10 c.c. of the fasting nonoxalated blood were utilized. The remainder of the blood was used for varied chemical blood determinations, such as serum lipid partitions, liver tests, serum protein fractions, and other blood chemistry findings[3].

Methods:—The blood samples were analyzed by the Durrum type of paper electrophoretic apparatus[9]. Detailed explanations of the procedures used[10,11] and the varied serum lipid partition methods were discussed in previous publications[12]. The method for the plasma antithrombin determinations has also been described in detail elsewhere[13,14].

Method of Paper Electrophoresis

The important steps in the procedure were that 10 millilambda (0.00001 c.c.) of serum was applied to Whatman 3 mm filter paper strips (run in duplicate). Eight filter paper strips (or specimens) were run at one time with a total time expenditure of one hour by the investigator. The Spinco-Durrum Tent type of paper electrophoretic apparatus was used[9,10]. The buffer solution was diethylbarbiturate, pH 8.6, ionic strength 0.05. The diethylbarbiturate buffer has a higher resolving power than the phosphate buffer. The latter cannot resolve alpha-1 from albumin. Eight paper strips were held taught and covered with a hood to prevent evaporation. Current of 1 ma per paper strip (total of 8 ma) was passed for 14 hours. The strips were fixed at 110°C.

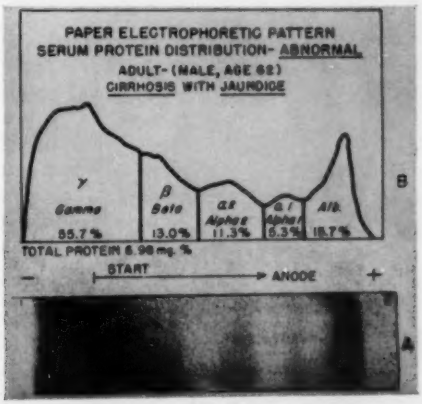


Fig. 2–Dyed filter paper electrophoretic strip and corresponding pattern of serum proteins. Patient 3, adult male, age 62. *Diagnosis:–Cirrhosis with jaundice.* Pattern shows markedly decreased albumin, slightly decreased beta, and markedly increased gamma components. A/G Ratio 0.18. Total protein 6.98 mg., and A/G Ratio 1.40 (Chemical determination). Plasma antithrombin titer very low (– – –). Liver biopsy showed marked cirrhosis.

Photoelectric Evaluation of Electrophoresis

Staining of filter paper strips:–The strips were stained with Amido-black 10B and destained with methanol acetic acid solution. This dye was used in place of the previous staining performed with bromphenolblue. It was easier for routine work. The quantitative comparison of the numerical values established for the various protein fractions is dependent on the condition that an equal amount of dye, for example, the Amido-black 10B, be taken up by the various protein fractions. This is better for Amido-black than for any other anionic dyes[8]. Before the strips were analyzed, the filter paper was immersed in mineral oil to make it more translucent. This procedure had a markedly favorable effect

on the accuracy of the results. It is important to make the strip transparent before measuring in order to obtain correct results[15,16].

Densitometry and planimetry:—After oiling, the strips were densitometered with Photovolt Model 525 A with a scanning motor, connected to a Varian Recorder. This was a much time saving device. The curves were planimetered to obtain the concentration values calculated from the areas corresponding to the peaks (Fig. 1).

Technical problems:—Control experiments of staining with dye performed under different conditions; for example, variations in dye concentration, types of dye, staining time, and the method of destaining, show that it is important

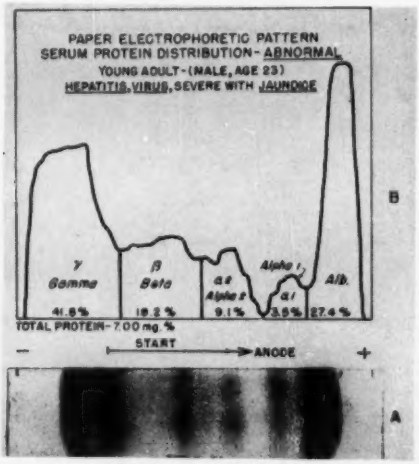


Fig. 3—Comparison of dyed filter electrophoretic strip (A), and corresponding densitometered and planimetered serum protein pattern. Patient 26, young adult male, age 23. *Diagnosis:—Hepatitis, virus,* Severe with *jaundice.* Pattern shows a markedly decreased albumin, slightly decreased alpha-2, and markedly increased gamma components. A/G Ratio 0.38. Total protein 7.00 mg per cent with A/G Ratio 0.52 (Chemical determination). Plasma antithrombin titer very low (– – –). High total cholesterol 430 and high lipids, 1.096 mg. per cent.

to control closely all of these variables if correct results are to be obtained. Protein staining, previously performed with bromphenol blue, was now done with Amido-black 10B, and destained with methanol-acetic acid solvent[10].

Variable quantitative results are due to inherent errors and factors in paper electrophoretic and dyeing procedures, rather than in the analysis of the final patterns[16]. Certain of these inherent errors may be minimized by careful attention to technic detail. Albumin "tailing", differential dye-binding of albumin and globulins, nonstaining of lipid components of lipoprotein complexes, and

nonvalidity of Beer's Law, represent problems peculiar to the paper electrophoretic technic[17].

Results

The list of chemical disturbances observed in liver disease is a long one and undoubtedly will become greater as metabolism in liver disease is studied more intensively. Technical advances within recent years have made more accurate protein fractionation possible by the more simplified paper electrophoresis. This laboratory procedure has given the clinician the possibility of detecting in a simple manner blood protein changes in numerous diseases, both as an aid in clinical diagnosis and in understanding the underlying physiological and pathological processes. Our interests lay in studying patients with hepatobiliary disease for further clinical evaluation of plasma antithrombin titer as a liver test, with simultaneous electrophoretic and other chemical determinations.

Paper Electrophoretic Patterns—Analysis

Serum protein distribution—normal:—A paper electrophoretic pattern of a normal human serum protein distribution may be noted in Figure 1. Usually, in the majority of cases a typical densiometer pattern reveals five components. New and abnormal components may be found as investigation progresses. The serum proteins occurred as five bands corresponding in the order of increasing mobility, to gamma, beta, alpha-2, alpha-1 globulins, and to albumin (Fig. 1). In some instances, beta-1 and beta-2 components were measured. Some bands included alpha-1 and alpha-2, with one component as alpha-2. We have designated beta-1 and beta-2 under one heading as "beta" component. The most densely stained portion was noted in the albumin fraction, less in the beta, and least in the other areas of alpha-1 and alpha-2 (Fig. 1). The individual serum protein components were represented as relative concentrations, expressed in percentages, and were within the range of normal values (Table I). The albumin/globulin ratio calculated from the relative percentage concentration of the electrophoretic components was 0.85. This was the method utilized for all of the patients, giving a mean normal, A/G ratio of 0.72 ± 0.29 (Table I). When chemical determinations were made on the same serum, the normal mean A/G ratio was 1.52 ± 0.25 (Table I). It has been noted by others that the A/G ratio as measured electrophoretically is lower than that obtained by chemical fractionation of the same sample [18,19,20].

Electrophoretic patterns—hepatic disease (Fig 2, Table I):—Albumin and gamma fractions:—It was noted that in practically 85 per cent of the patients with liver disease there was a decrease in the albumin component, with a mean average of 29.2 per cent ± 6.8 as compared to the normal of 42.5 per cent ± 3.9, with a concomitant increase of the gamma component to 33.9 per cent ± 8.8 (normal 22.1 per cent ± 2.6).

TABLE I

PAPER ELECTROPHORETIC PATTERNS (PERCENTAGES OF TOTAL PLANIMETERED AREA); CHEMICAL DETERMINATIONS (GM. %). WITH MEAN AND STANDARD DEVIATION VALUES OF SERUM PROTEINS IN PATIENTS WITH HEPATIC DISEASE, AND PLASMA ANTITHROMBIN TITER LEVELS

		Serum Proteins										Plasma
		Electrophoretic						Chemical				Chemical
No. of Patient	Age of Patient	Albumin	Alpha-1	Alpha-2	Beta	Gamma	A/G Ratio	Total Proteins	Albumin	Globulin	A/G Ratio	Plasma Antithrombin Titer Level*
Normals												
Mean		42.5	5.1	11.3	19.0	22.1	0.72	7.01	4.23	2.78	1.52	Normal (N)
Stand. Dev.		± 3.9	± 1.8	± 3.3	± 2.7	± 2.6	±0.29	±0.51	±0.48	±0.34	±0.25	
1	80	17.1	10.9	13.9	27.5	30.5	0.21	7.64	4.65	2.99	1.5	– – –
2	84	35.0	6.0	[illegible].1	14.4	28.5	0.54	6.98	4.15	2.83	1.4	N
3	62	15.0	5.3	11.3	13.0	55.7	0.18	6.98	4.15	2.83	1.4	– – –
4	64	26.1	3.5	8.0	20.3	42.0	0.35	7.33	4.62	2.71	1.7	– – –
5	45	22.0	6.7	11.7	11.4	48.3	0.25	6.84	4.19	2.65	1.6	– – –
6	51	26.4	8.1	12.0	13.5	40.0	0.36	7.53	4.60	2.93	1.5	– –
7	77	24.3	5.2	9.7	26.9	39.5	0.30	6.10	2.90	3.20	0.9	– –
8	51	40.2	6.5	11.2	17.3	24.8	0.67	5.30	2.40	2.70	0.8	– – –
9	79	29.7	7.2	12.8	11.5	38.7	0.42	7.92	4.29	3.63	1.02	– – –
10	79	27.3	8.7	5.4	17.4	41.4	0.37	5.75	2.49	2.66	1.10	– –
11	61	32.8	7.1	17.3	23.8	19.0	0.49	5.88	3.60	2.28	1.60	– – –
12	23	27.7	8.7	10.5	18.8	34.5	0.38	6.46	4.00	2.46	1.60	N

13	69	23.6	4.6	25.6	18.6	27.6	0.31	6.18	3.69	2.49	1.50	– –
14	84	42.7	5.2	12.1	17.1	22.9	0.75	7.18	4.10	3.08	1.30	N
15	73	40.3	4.4	6.8	24.7	23.8	0.68	7.27	4.62	2.65	1.70	N
16	46	44.2	7.6	5.7	18.7	23.8	0.79	6.94	4.09	2.85	1.40	N
17	68	26.7	8.6	20.4	12.7	31.6	0.36	6.83	3.40	3.43	1.10	N
18	65	34.6	4.5	9.9	22.0	29.0	0.34	6.72	2.95	3.77	0.99	N
19	67	22.4	6.8	10.1	14.7	46.1	0.28	7.94	3.77	4.17	0.90	–
20	84	28.4	6.8	13.5	14.4	36.8	0.40	5.94	2.95	2.99	0.99	– –
21	91	35.2	9.0	20.9	13.3	21.6	0.54	5.73	2.97	2.76	1.01	N
22	23	33.5	3.5	11.0	21.2	30.8	0.50	7.15	3.79	3.36	1.10	N
23	45	32.0	3.8	9.4	28.4	29.5	0.45	7.02	3.34	3.68	0.91	N
24	34	19.4	5.1	15.9	31.4	28.2	0.24	4.75	2.05	2.70	0.76	–
25	55	25.3	9.8	6.2	22.9	38.6	0.33	6.20	3.26	2.94	1.20	N
26	23	27.4	3.5	9.1	18.2	41.8	0.38	7.00	2.40	4.60	0.52	– – –
27	55	25.9	7.3	13.8	25.1	27.4	0.35	5.90	3.02	2.88	1.10	N
28	24	31.6	3.1	5.7	15.2	47.3	0.44	7.05	2.55	4.50	0.57	–
Patients with Liver Disease												
Mean	57	29.2	6.3	11.6	18.6	33.9	0.42	6.68	3.53	3.10	1.18	
Stand. Dev.		± 6.8	± 1.8	± 3.8	± 4.8	± 8.8	±0.14	±0.64	±0.55	±0.59	±0.29	

*Normal (N)=Normal Clotting Time at the five-minute incubation period ranges from 20 to 25 seconds. Decreased Antithrombin Titer Level (–).Defined in terms of the percentage decrease in clotting time of unknown sample compared with normal at the five minute incubation period [Depressed (–); Moderate (– –); Very Low (– – –) Ref. 2].

Alpha-1 and alpha-2 components:—The alpha-2 component (53 per cent) varied more from the mean normal than the alpha-1 group (3 per cent), yet their respective mean values did not. It was of interest to note that the mean for alpha-1 group in hepatic patients (6.3 per cent ± 1.8) was more than the normal of (5.1 ± 1.8). The results of alpha-1 and alpha-2 globulins revealed no additional information in the hepatic diseased patients (Table I, Figs. 2, 3, 4, 5).

Beta component:—This fraction of the globulins showed normal values for 43 per cent of the patients, with a 30 per cent increase and 30 per cent decrease. The mean values of 18.6 per cent ± 4.8 was slightly less than that of the normals (19.0 per cent ± 2.7). The beta globulin was not increased in most cases as observed by others.

Albumin/globulin ratio:—As mentioned above, the normal ratio reported herein of 0.72 was obtained by utilizing the relative concentration of the components from the electrophoretic pattern (Fig. 1). It was higher, 1.52 ± 0.25, when the chemical method was performed (Table I). Even with this method, the mean value for the A/G ratio in the liver patients (0.42 ± 0.14) was very much lower than the normal, of 0.72 ± 0.29 (Table I). Since paper electrophoretic analysis is to be considered a semiquantitative procedure, the albumin levels tend to be appreciably lower than those by chemical partitions; and even by the moving boundary electrophoresis of Tiselius. This accounts for the discrepancy in values. Many question the value of the A/G ratio for clinical use and they maintain that the use of the term "A/G ratio" is misleading, worthless, and should be abandoned[21].

Chemical serum proteins:—The mean values showed the total proteins of 6.68 mg. per cent ± 0.64 not much lower than the normal of 7.01 mg. per cent ± 0.51. This relatively high value of total proteins alone did not reveal the serum protein change which occurred in hepatic disturbance. The A/G ratio by this method of 1.18 ± 0.29 was less than the normal of 1.52 ± 0.25 (Table I). The electrophoretic experiment, however, revealed more of the underlying disturbed physiology with its effect upon the albumin and the gamma globulin components particularly. The albumin was markedly diminished, while the gamma globulin was increased—resulting in a very low A/G ratio of 0.42, compared to the electrophoretic normal of 0.72, a decrease of about 58 per cent (Figs. 2, 3).

Serum lipid fractions (Table II):—These values varied. The highest cholesterol and total serum lipids were encountered in the patients with cirrhosis and jaundice (Fig. 2) or cirrhosis with diabetes mellitus (Patient 19). Severe hepatitis also revealed increased values (Patient 26, Fig. 3). These above conditions showed higher gamma globulin values (Figs. 2, 3). Cirrhotic cases in coma resulted in lower values for all partitions. One of the authors (A.A.G.) previously showed that the hyperlipemia in jaundiced patients was correlated directly with the icterus and hyperbilirubinemia[3]. The mean values of the total serum

TABLE II

ARITHMETICAL MEAN AND STANDARD DEVIATION VALUES OF SERUM LIPID PARTITIONS IN PATIENTS WITH HEPATIC DISTURBANCES AND NORMAL INDIVIDUALS. VALUES EXPRESSED IN MILLIGRAMS PER 100 ML. SERUM, AND PERCENTAGES IN TERMS OF TOTAL LIPID VALUES

Lipid Fractions	Normals		Hepatic Dsease	
	← Milligrams		Per Cent	→
Cholesterol	Mean	Stand. Dev.*	Mean	Stand. Dev.
Total	197	41.1	283	61
Esters	121	27.0	162	47
% of Total Cholesterol	61.2	–	57.2	–
Free Cholesterol	76	16.5	121	57
% of Total Cholesterol	38.8	–	42.8	–
**Esterified Cholesterol	202	32	271	90
Lipid Phosphorus	8.6	0.8	7.1	0.8
Phospholipid	218	31.0	180.0	23
Neutral Fats	365	99	197.0	87
Total Lipids	861	78	756	173
Ratio Phospholipids to Total Cholesterol (P/c Ratio–Units)	1.10	0.14	0.63	0.38
Lipid Fractions		Percentage of	Total Lipids	
Free Cholesterol	9.1	± 1.76	15.7	± 4.41
Esterified Cholesterol	23.5	± 5.66	35.2	± 8.60
Phospholipids	25.3	± 3.58	23.4	± 4.46
Neutral Fats	42.1	± 9.36	25.7	±11.0
Total Proteins:	7.01	± 0.51	6.68	0.64

*S.D.=Standard Deviation

**Factor 1.67 utilized to multiply the Cholesterol esters to obtain the esterified Cholesterol values. (Refs. 3, 12)

lipids of all the hepatic cases of 756 mg. per cent was less than the normal of 861 per cent mg. (Table II). The serum lipid fraction percentages in all the hepatic patients showed the mean values of the phospholipids and neutral fats to be less than the normal, the free cholesterol and esterified cholesterol, increased. In spite of such variations, the ratio of phospholipids to total cholesterol was less than normal. Patients with cirrhosis in whom the lipid values were subnormal with a degree of lowering was a good index of liver severity. There were no cases of obstructive jaundice nor cholangiolitic cirrhosis in the series.

Plasma antithrombin titer:—The sensitivity of many tests for a specific liver function yield findings often inconsistent with the clinical state of the patient. A

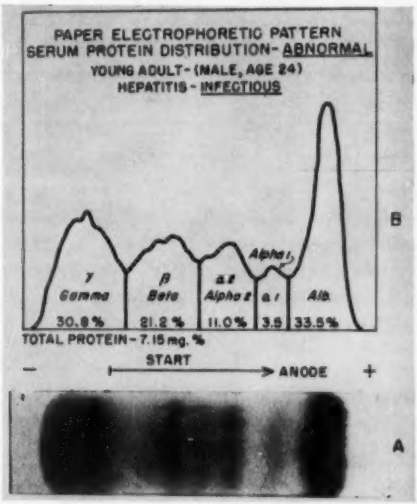


Fig. 4—Dyed filter paper electrophoretic strip (A) and corresponding pattern (B) of serum proteins. Patient 22, young adult male, age 24. *Diagnosis:—Hepatitis-infectious, in a narcotic addict.* Pattern shows slightly diminished albumin and moderately increased gamma components. A/G Ratio 0.50. Total protein 7.15 mg. per cent, with A/G Ratio 1.10 (Chemical determination). Plasma antithrombin titer was normal. Liver biopsy was normal.

liver function test whose titer specifically parallels variations in the severity and extent of liver cell damage should therefore prove valuable. It was propounded by one of the authors (I.I.) that the level of antithrombin is conditioned by the degree of functional overall dissociation of the liver cell in both incipient and advanced stages of hepatic insufficiency. It was advocated that inasmuch as antithrombin diminution occurs in progressively severe stages of liver impairment, the test may be used as an *index of severity.* It was considered this procedure should be tried in patients with evidence of liver disease, for its usefulness as a liver test.

Comparative antithrombin titer and gamma globulin changes:–The gamma globulin component showed the greatest and most frequent changes from the paper electrophoretic procedure in the patients with liver disease. It was evident that the plasma antithrombin titer level changes must be compared to the changes in the serum gamma globulin percentage values. In the 28 patients studied with the electrophoretic experiment, the antithrombin titer (A.T.T.) showed decreased values in 16 patients (57.1 per cent); and normal values in the other 12 patients (42.9 per cent) (Table III). Of these 16 patients, however, there were 14 showing simultaneous gamma globulin changes (50 per cent). The lowest A.T.T. changes (– – –) with the highest (+ + +) gamma globulin increase were evident in only six patients (21.4 per cent). The gamma values

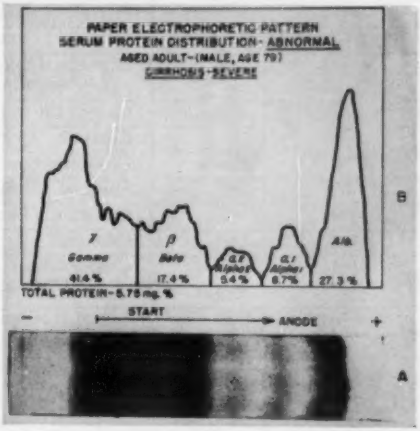


Fig. 5–Comparison of dyed filter electrophoretic strip (A), and corresponding electrophoretic pattern (B) of serum proteins. Patient 10, adult male, age 79. *Diagnosis:–Cirrhosis-severe.* Pattern shows moderately diminished albumin and alpha-2, with markedly increased gamma globulin components. A/G Ratio was 0.37. Total proteins 5.75 mg. per cent, with A/G Ratio of 1.10 (Chemical determination). Plasma antithrombin titer was markedly low (– – –). Exitus occurred.

were normal in six patients (21.4 per cent), and abnormal in 22 patients (78.6 per cent) (Table III).

The gamma globulin level did not foretell in some patients the severity of the condition as the markedly decreased (– – –) antithrombin level (Patients 1, 8, 11, 13). The same was true for the A.T.T. level (Patients 19, 28).

The electrophoretic pattern with change in the gamma globulin component was of little aid in explaining the mechanism of the effect or the change caused by the plasma antithrombin titer.

In a separate group of 22 patients, in whom liver tests and the A.T.T. were done without any electrophoresis, there were seven normal values (31.8 per

TABLE III

CHANGES IN VALUES OF PLASMA ANTITHROMBIN TITER LEVELS COMPARED TO CHANGES IN SERUM GAMMA GLOBULIN FROM PAPER ELECTROPHORETIC PATTERNS IN PATIENTS WITH LIVER DISEASE

No.	Age	Plasma Anti-thrombin Titer Level*	Serum Gamma Globulin** (Paper Electrophoresis)	Add'l Clinical Procedures	Clinical Diagnosis
3	62	− − −	+++	Autopsy	Cirrhosis; Jaundice
4	64	− − −	+++	Biopsy	Cirrhosis
5	45	− − −	+++	Surgery	Cirrhosis; Jaundice; Gastric Malignancy
9	79	− − −	+++	Surgery	Hepatic abscess; Gastric Malignancy
10	79	− − −	+++	Exitus	Cirrhosis; Coma
26	23	− − −	+++		Hepatitis (Severe) (Virus); Jaundice; (Improved)
1	80	− − −	+	Exitus	Cancer Liver; Stomach; Anemia
13	69	− − −	+		Cirrhosis; Anemia
8	51	− − −	N	Exitus	Cirrhosis; Coma
11	61	− − −	N		Cardiac; Cirrhosis
6	51	− −	++		Cirrhosis; (Laennec's type)
7	77	− −	++	Biopsy	Cirrhosis
20	84	− −	++		Cancer Liver; Cancer Lung (?)
19	67	−	+++	Exitus	Cirrhosis; Diabetes Mellitus
28	24	−	+++		Severe Hemophysis; Jaundice
24	34	−	+		Cirrhosis
12	23	N	++		Hepatitis; (Narcotic Addiction)
17	68	N	++		Cirrhosis; Diabetes Mellitus
22	23	N	+++	Negative Biopsy	Addict Narcotic; Hepatitis
25	55	N	++	Surgery	Cardiac Failure; Enlarged Liver; Cancer Stomach
2	84	N	+		Liver Enlargement; Addison-Biermer's Anemia
18	65	N	+		Cirrhosis
23	45	N	+		Cirrhosis; Diabetes Mellitus
27	55	N	+		Liver Enlarged; Jaundice; Diabetes Mellitus
14	84	N	N		Liver Enlargement; Cardiac
15	73	N	N		Liver Enlargement; Cardiac
16	46	N	N		Cirrhosis; Pyelonephritis
21	91	N	N		Jaundice; Generalized Arteriosclerosis
Av.	57				

*Normal (N)=Normal Clotting Time at the 5-minute incubation period ranges from 20 to 25 seconds. Decreased antithrombin titer level (−). Defined in terms of the per cent decrease in clotting time of unknown sample compared with normal at the 5-minute incubation period. (Depressed −), (Moderate − −), (Very Low − − −) Ref. 2.

**Serum Gamma Globulin changes (Values Mg. %) Normal N=(20-25); Increased +=(25-30); ++ (31-40); +++ (40 and above) (See Table I).

TABLE IV

PLASMA ANTITHROMBIN TITER LEVEL AND OTHER LIVER TESTS IN PATIENTS WITH LIVER AND PANCREATIC (MALIGNANT) DISEASES

No.	Age	Sex	Diagnosis	Antithrombin Titer Level	Cephalin Flocculation	Thymol Turbidity	Prothrombine Time	Icterus Index	Bilirubin	Alkaline Phosphatose	Cholesterol			Albumin	Globulin	Total Protein	A/G Ratio	
											Total	Esters	60% Value of Total					
29	55	M	Cancer pancreas	+++														
30	62	M	Cancer pylorus; Cancer pancreas	+++														
31	69	M	Cancer pancreas	++		1.0				74.2	432	272	259	4.51	2.49	7.00	1.8	
32	73	F	Cirrhosis liver	+	Neg.						238	125	143	2.9	3.0	5.9	0.96	
33	70	M	Gastric Malignancy	+	+	Neg.								3.0	2.1	5.1	1.43	
34	43	F	Epilepsy	N														
35	67	M	Cirrhosis; Diabetes Mellitus	N							252	212	151	3.5	3.3	6.8	1.06	
36	51	F	Cirrhosis; C.V.A.	N	3+						200	118	120	2.3	4.2	6.5	0.55	
37	50	F	Cirrhosis; Jaundice	N	4+			94			114	30	68	2.0	4.6	6.6	0.44	
38	24	M	Serum Jaundice	N														
39	42	M	Postcholecystectomy	N	Neg.	2.0				13.0	210	180	126	4.32	2.16	6.48	1.95	
40	48	F	Epilepsy	N	4+					4.1	174	87	104	3.92	1.31	5.23	2.97	Died
41	49	M	Cirrhosis	–	4+	9.2	4.2			22	328	135	196	1.3	4.0	5.3	0.32	
42	16	M	Infectious Hepatitis	–	Neg.	1.1					250	195	150	3.2	2.1	5.3	1.52	
43	70	M	Cirrhosis; Jaundice	–										1.9	5.3	7.2	0.36	
44	55	M	Cirrhosis; Jaundice	–										3.6	3.6	7.2	1.00	
45	64	M	Cardiac; Ascites	–							226	143	135	2.7	3.8	6.5	0.71	
46	51	M	Cirrhosis	–														
47	27	M	Infectious Hepatitis	– –	4+	2.7					208	88	120	4.2	1.8	6.0	2.33	
48	42	M	Liver Disease	– – –														
49	58	F	Cirrhosis–Coma	– – –														
50	18	F	Hepatitis	– – –		2.2			12.8	1.0	140	31	84	3.0	3.8	6.8	0.80	

cent); 10 low levels (45.4 per cent); and five elevated (22.8 per cent). The latter patients showed pancreatic involvement, especially malignancy (Table IV).

In the combined group of 50 patients, the A.T.T. level showed a change in 31 patients (62.0 per cent) and normal levels in 19 patients (38.0 per cent). The gamma globulin component showed change in 22 patients from the 28 (78.6 per cent) and normal values in six patients (21.4 per cent). Thus, comparatively, the serum gamma globulin component showed change in 78.6 per cent; the plasma antithrombin titer level in 62.0 per cent of patients with hepatic disturbance.

TABLE V

PATIENTS DIVIDED INTO GROUP VALUES DEVIATING FROM NORMAL AND THE NUMBER OF EACH

	− − −	− −	−	Normal	+	+ +	+ + +
Albumin	below 20 (3)	20-29 (14)	30-39 (7)	40-45 (4)	Above 45	0	0
Alpha-1	0	0	0	3-8 (22)	9-12 (6)	Above 12	0
Alpha-2	0	Below 7 (4)	7-9 (5)	10-15 (13)	16-20 (5)	Above 20 (1)	0
Beta	0	0	Below 17 (10)	17-22 (10)	23-25 (4)	Above 25 (4)	0
Gamma	0	0	Below 20	20-25 (6)	26-30 (8)	31-40 (7)	Above 40 (7)

STATISTICAL ANALYSIS OF DATA

Paper electrophoretic components:—This evaluation was based on data for 28 patients with known liver disorders. The objective was to select positions of the protein pattern obtained by paper electrophoresis which showed consistent differences from normal values and try to correlate these differences with values obtained for various chemical determinations on blood from these patients. The initial step was to stratify the patients into groups which showed marked departures from normal. This classification was based on the values given in Table V with the number of cases falling into each group given in parenthesis.

It may be readily seen that for alpha-1 over two-thirds of the patients exhibited normal levels, while for alpha-2 and beta there were almost as many values above normal as below normal, so that no consistent relationship could

be detected. For albumin, most patients (85 per cent) showed below normal levels while 75 per cent showed above normal values for gamma. This suggested that these two attributes would be the most promising portions of the electrophoretic patterns for proteins for further evaluation. Therefore a two-way frequency distribution of the gamma and albumin levels in the patients was considered for any correlation. The values are shown in Table VI.

The correlation between albumin values and gamma values was $r = +.63$*, indicating a moderate relationship existed between the two values. While such a correlation values is sufficient to reject the hypothesis of no relationship, it still leaves much to be desired, in that only about 40 per cent of the variability in the values is accounted for through this relationship†. Since correlation coefficients are nondimensional, they are of limited value in evaluating the detail of information given in this study and as such were not used.

TABLE VI

A Two-Way Frequency Distribution of the Serum Gamma and Albumin Cases

			Gamma Globulin				
			Normal	+	++	+++	Total
		Normal	4				4
		−	2	4		1	7
Albumin		−−		2	7	5	14
		−−−		2		1	3
	Total		6	8	7	7	28

To measure the association between albumin and gamma values and the other determinations, mean values for each characteristic were computed for each of the groups of albumin and gamma levels delineated previously. The standard deviation for the complete set of measurements was also computed to provide a basis for comparing some of the results obtained. Estimation of means and standard deviations for subgroups was avoided because of the small numbers of observations and relative instability of such estimates. The table of mean values is presented below (Table VII).

The results given in Table VII were evaluated by seeing if any consistent trends were shown and noting if any single distinct difference could be detected in the absence of a trend.

*Coefficient of correlation.

†This is estimated from $r^2=(.63)^2=.397$.

TABLE VII

MEAN VALUES FOR DETERMINATIONS OF SELECTED ITEMS FOR 28 PATIENTS WITH LIVER DISORDERS, BY LEVELS OF SERUM ALBUMIN AND GAMMA DETERMINATION (PAPER ELECTROPHORETIC METHOD)

Item	Albumin				Gamma				All Cases	
	Normal	–	– –	– – –	Normal	+	++	+++	Mean	Std. Dev.
No. Patients	4	7	14	3	6	8	7	7	28	
Albumin	41.8	33.5	27.9	17.2	39.2	27.6	26.9	24.6	29.2	6.8
Alpha-1	5.9	5.3	6.8	7.1	6.6	5.7	7.8	5.4	6.3	1.8
Alpha-2	8.9	12.5	11.5	13.7	12.3	14.4	11.0	8.4	11.6	3.8
Beta	19.4	20.1	16.5	23.7	19.1	23.6	15.0	16.1	18.6	4.8
Gamma	23.8	29.8	38.8	38.1	22.7	28.9	37.1	46.0	33.9	8.8
A/G-Ratio	.72	.47	.35	.21	.65	.37	.36	.32	.42	.14
Cholesterol Total	208	298	312	310	209	285	275	390	283	61
Ester	127	149	186	187	127	148	175	219	162	47
Free	81	149	126	123	82	137	100	171	121	57
Lipid Phosphorus	7.8	7.3	7.0	6.8	7.7	6.8	6.5	7.6	7.1	.8
Phospholipids	196	179	179	170	193	169	162	199	180	23
Esterified Cholesterol*	239	249	281	312	230	247	229	365	271	90
Neutral Fats	212	192	198	189	198	222	231	138	197	87
Total Lipids	731	708	798	794	706	722	698	899	756	173
Total Protein	6.67	6.64	6.76	6.46	6.38	6.54	6.81	6.98	6.68	.64

*Factor 1.67 x cholesterol ester values = Esterified cholesterol[3].

The statistical significance was obtained from the "t-test", as follows:

$$t = \frac{M_1 - M_2}{\sqrt{\frac{1}{N}(S_1^2 + S_2^2)}}$$

M = Mean values between paired observations.
N = Number of patients in each group.
S = Standard deviations of paired observations.

Level of significance: The null hypothesis was rejected at the per cent level. The 5 per cent level was considered of only borderline significance by the "t-test".

The findings of the analysis were as follows*:

Albumin and gamma:–The albumin mean for the gamma levels showed a distinct difference between normal and + groups, with no difference between the + groups. For the albumin groups, however, there appeared to be a consistent increase in gamma mean through the – – level, but not between the higher levels. These results suggest that there is more difficulty in detecting differences among the extreme conditions in albumin and gamma than between normal and abnormal values in general.

Alpha-1 and alpha-2:–There appeared to be no consistent change in alpha-1 and alpha-2 with varying albumin and gamma groups. This is consistent with the failure of any distinct deviations by the 28 patients from normal values for alpha-1 and alpha-2.

Beta group:–The beta means were erratic for the albumin groups, but the beta mean for normal and + gamma groups were somewhat higher than for ++ and +++ groups, suggesting a slight relationship between these attributes.

A/G ratio:–There was a consistent downward trend in A/G ratio for the albumin groups, while for the gamma groups a wide difference was noted for normal and increased groups, but no difference among those groups with high gamma. Since A/G ratio is based on the [albumin]/[alpha-1 + alpha-2 + beta + gamma] values, it is possible that in the groups with high gamma, there may be some compensating changes in the alpha-1, alpha-2, and beta components. Another explanation, however, is that A/G ratio is dependent on the albumin level primarily and the means for the A/G ratio closely parallel the means for albumin for the albumin and gamma classes.

*Differences between means which exceed one and one-half times the standard deviation for the data may be regarded as an indication of an event which has only a small probability of happening due to chance alone (i.e. a statistically significant difference).

Serum lipid fractions:—Cholesterol:—Individuals with abnormal albumin or gamma levels had higher cholesterol than normal groups.

No difference in cholesterol was evident for the albumin groups, but the highest gamma group had a significantly higher cholesterol than the + and ++ groups. This may indicate gamma differences are more closely associated with cholesterol level than are albumin differences.

There was a general increase in cholesterol esters for both albumin and gamma groups, while there was no definite relationship for free esters. The pattern observed for total cholesterol, therefore, is due to the differences in the esters and the varying amounts of free cholesterol tend to modify the effects of the esters in the total cholesterol pattern.

Lipid phosphorus:—Although there was a downward trend in lipid phosphorus for the albumin groups and a mixed relationship for the gamma groups, the differences were not sufficiently longer than the standard deviation to permit any general conclusions.

Phospholipids:—Phospholipids were lower for all abnormal albumin groups than for normal, while no useful pattern was found for the gamma groups.

The esterified cholesterol was higher for the extreme classes of albumin and gamma, while there was no difference between normal and the closest abnormal group.

Neutral fats:—Neutral fats were very low for the +++ gamma group, but otherwise no differences were observable for the albumin and gamma groups. Neutral fats were generally lower for the patients than for normal subjects.

Total lipids:—There was considerable variability in the amount of total lipids for several of the albumin and gamma classes, but these were attributed to chance in view of the high standard deviation. Total lipids for patients were below levels for normals in general.

Total protein:—Total protein increased with gamma level, but no clear relationship existed for the albumin levels.

Plasma antithrombin titer levels:—The antithrombin titer did not show any real discrimination, since 12 of the 28 patients had normal reactions, and of the 10 patients in the lowest antithrombin titer ratings, two showed normal and two showed mild deviation for the albumin and gamma components (Table III). Supplementary data for 22 liver patients not included in this study, with electrophoresis, showed seven cases of normal titer levels (31.8 per cent). In the remainder, 15 cases, there were five cases of an elevated titer level, in pancreatic-carcinoma. The remaining revealed three cases of a very low titer (— — —) and seven of a moderate level. This showed that the antithrombin titer level produced changes in 62 per cent of liver patients compared to 78.6 per cent of gamma globulin changes.

A two-way frequency distribution of the antithrombin titer level and the serum gamma globulin indicated no definite relationship between the two values (Table VIII).

Filter Paper Electrophoresis

A clinical laboratory test:–Electrophoresis has proved to be a reliable analytical method for the study of varied specific constituents in both the medical and nonmedical professions. Such examples are proteins, lipids, carbohydrates, vitamins, enzymes, and heavy metals. The extreme simplicity, inexpensiveness and time-saving of the apparatus required for the electrophoretic separation of serum proteins and lipoproteins[10] on filter paper make it possible for such a specialized diagnostic equipment to be available for routine laboratory procedure.

TABLE VIII

Two-way Frequency Distribution of the Plasma Antithrombin Titer Levels and of Serum Gamma Globulin Cases

		Serum Gamma Globulins (Electrophoresis)				
		Normal	+	++	+++	Total
Plasma Antithrombin Titer Level (Chemical Method)	Normal	4	4	4		12
	–		1		2	3
	– –			3		3
	– – –	2	2		6	10
	Total	6	7	7	8	28

Clinical significance:–The clinical significance of filter paper electrophoresis for the physician may be two-fold. Firstly, it may offer information about the underlying disturbed physiology produced by the disease. This may be reflected in the abnormalities of the serum protein pattern (Figs. 2, 3, 5) thus, helping the physicians to be guided by the prognosis, severity, or type of disease. Secondly, it may produce diagnostic information as to the particular disease or group of diseases associated with the type of abnormal protein distribution. Often simple inspection of the paper strip may demonstrate clearly the nature of the serum protein abnormally present, without quantitation of the pattern, e.g. hypogammaglobulinemia, multiple myeloma, infectious hepatitis. Such a procedure, however, would not be accurate in detecting moderate deviations from normal and would be less informative than the quantitative procedure.

Hepatic disease disturbances:—Our interest in this study was mostly in understanding the mechanism of the disturbed physiology and the abnormal electrophoretic components obtained in liver disease. In addition, to clinically evaluate further the significance of the plasma antithrombin titer as a clinical test for the severity of the liver disease and if its action or property could be correlated by the electrophoretic procedure. This test involves the major enzyme system whose antithrombin titer specifically parallels variations in the severity and extent of liver cell damage. Since the functions of the liver are many and varied, it was not possible to discuss all of them.

It is well recognized that changes in electrophoretic patterns of serum or plasma proteins occur in various types of liver diseases[6,20,22-26].

Protein fractionation—components in blood clotting:—The liver has a dominant role in protein synthesis. It is the source of plasma albumin and fibrinogen. Probably proteins other than fibrinogen involved in the clotting of blood also originate in the liver, e.g., antithrombin, and antithrombinogen[13,14].

The delayed clotting of blood of many patients with liver disease is the result of a combination of defects. There may be diminished prothrombin, deficiency of accelerator globulin (Ac-globulin), Factor V, labile factor, and other factors. Fibrinogen concentration may be low and fibrinolysin activity of plasma be increased. Low antithrombin titers in serum hepatitis have been reported[13,14]. It is the source of important components included in the alpha and beta globulins.

Indeed, by using paper electrophoresis to separate the components of plasma proteins, various clotting activities in saline eluates of segments of the filter paper have been tested[27]. These writers observed that prothrombin coincided with the alpha-2 component; antithrombin and thrombin between alpha-2 and beta-globulins. Another protein component that has aroused recent renewed interest is fibrinogen, a globulin, found between beta and gamma. It is formed in the liver. Other components observed were plasmin, an enzyme, associated with the globulins, and antiplasmin, an inhibitor, associated with albumin. Plasminogen, an inactive enzyme-precursor, exists in the blood.

The above varied protein components have been mentioned because of the bearing they have in explaining the action of the plasma antithrombin titer and its change in liver diseases.

Blood clot mechanism—trypsin upon fibrin:—The fibrinolysis phenomenon (the splitting up of fibrin by enzyme action) of clotted blood by the action of trypsin upon fibrin is shown in Table IX.

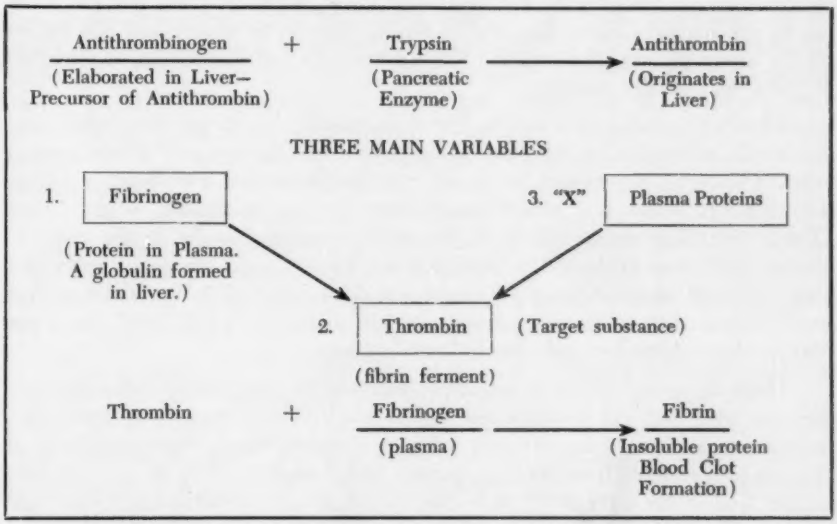
Fibrinogen, a soluble protein in the blood plasma, by action of thrombin (fibrin ferment) is converted into fibrin, thus producing clotting of the blood.

Fibrin is an insoluble protein and forms the essential portion of the blood clot (Table IX).

"Antithrombinogen", the biochemical precursor of antithrombin, is elaborated by the liver cell under normal physiologic conditions. "Antithrombinogen" requires pancreatic trypsin for enzymatic conversion into antithrombin; but the actual site of this biochemical reaction was unknown (Table IX). Antithrombin is formed in the liver. When one adds thrombin (fibrin ferment) to plasma, which contains the protein fibrinogen, a clot is formed (Table IX). There are different types of clots. In patients with increased plasma antithrombin titer level, plasma takes more time to clot and the clots which form are more fragile than normal.

TABLE IX

THE FIBRINOLYSIS PHENOMENON OF CLOTTED BLOOD BY THE ACTION OF TRYPSIN UPON FIBRIN



Relationship between antithrombin titer and gamma globulin:–In the combined group of 50 patients with liver disease, the antithrombin titer level showed an abnormal response in 62 per cent of the cases. The gamma globulin component was elevated 78.6 per cent in 22 out of the 28 patients in whom the electrophoresis was performed (Tables III and IV, Figs. 2, 3, 5). The antithrombin titer did not show any real discrimination, since 12 of the 28 patients had normal reactions. A two-way frequency distribution of the plasma antithrombin titer level and the serum gamma globulin would indicate no definite relationship between the two values (Table VIII). Such comparisons do not reveal the action nor clinical significance of such a test.

Plasma antithrombin titer level as a liver test:—The protein constituents, besides antithrombin, comprising the coagulation mechanism, become involved in profound impairment of protein synthesis. It is noteworthy, however, that antithrombin is among the last of the clotting constituents to show impaired synthesis following widespread liver cell damage. The plasma antithrombin titer was found to be depressed in patients with hepatic insufficiency, of progressive severity. For this reason it was suggested (I.I.) its assay may become a highly accurate indicator of severe, progressive diffuse hepatic cellular neurosis (stages of hepatic insufficiency). *The test should be used as an index of severity.*

Paper Electrophoretic Components

Albumin and gamma:—The composition of the serum or plasma proteins plays an important role in numerous diseases, especially in hepatic disturbances. This has been definitely demonstrated by the determination of protein fractions by various apparatuses and electrophoresis. Only in this way has it been possible to get a good idea of the role of serum proteins in health and disease, to clarify many disease pictures, and an understanding of the clinical mechanism of the serum-lability reactions.

By this method, it was shown that the albumin was 85 per cent below normal levels, while the serum gamma component was 75 per cent above normal values (Table I). A two-way frequency distribution showed a moderate relationship between these two serum components by the coefficient of correlation (Table VI). The mean values of the various selected items in the patients (Table VII) were evaluated by seeing if any consistent trends were shown and notice of any simple distinct difference could be detected in the absence of a trend. The statistical significance was obtained from the "t-test", with the 5 per cent level considered of only borderline significance.

There appeared to be a consistent increase in the gamma mean through the −− level, but not between the higher levels. These results suggested that there is more difficulty in detecting differences among the extreme conditions in albumin and gamma, than between normal and abnormal values in general. This implies that in the later stage, it is easy to tell when the patient has abnormal values without their telling the extensiveness. In the early stage this difficulty is not so pronounced.

The alpha and beta components:—There appeared to be no consistent change in the alpha-1 and alpha-2 with varying albumin and gamma groups. The alpha group was increased in 6.3 per cent of the hepatic diseased cases. The results of the alpha-1 and alpha-2 globulins revealed no additional information (Table I). The increase in the alpha component with a decrease in the albumin was not observed as by others[22].

The beta globulin was not increased in most cases. The beta means were erratic for the albumin groups, yet there was a suggestion of a slight relationship

between the beta for normal and + albumin and beta groups. Serum lipid concentration has variations which are said to influence the electrophoretic pattern primarily because the lipoproteins migrate with the beta globulin. The results herein did not show any significant relation between the beta globulin levels and the total cholesterol values (Table VII).

Albumin/globulin ratio:—The albumin levels by electrophoresis are lower than those by chemical partitions, and even by the moving boundary electrophoresis. This accounts for lower A/G ratio values obtained normally. The A/G ratio was very low when compared to the normals. There was a consistent downward trend in the A/G ratio. This change may be explained by the fact that the A/G ratio is dependent on the albumin level primarily, and the means for the A/G ratio closely parallel the means for albumin for the albumin and gamma classes.

Serum lipid fractions (Tables II, VII):—Individuals with abnormal albumin and gamma levels had higher cholesterol than normal groups. The gamma differences were more closely associated with cholesterol level than the albumin differences. The pattern observed for total cholesterol was due to the differences in the esters and the varying amounts of free cholesterol tend to modify the effects of the esters in the total cholesterol patterns. The neutral fats were very low for +++ gamma groups. Neutral fats and total lipids were generally lower for the hepatic patients than for normal subjects. One of the authors (A.A.G.) mentioned that lipid changes in cirrhosis of the liver must be differentiated whether jaundice is present or not, since the hyperlipemia in jaundiced patients were correlated with the icterus and hyperbilirubinemia. These values further corroborated and observation that all serum lipid fractions must be determined to evaluate a true disturbance in lipid metabolism[3].

Total protein:—The chemical determination of the protein fractions showed the total protein to be increased with the gamma level, but no clear relationship existed for the albumin levels. It has been definitely shown that such chemical determinations are less accurate and often may be misleading, especially in liver diseases. The electrophoresis is of more value to the clinician for understanding the underlying pathological liver changes.

Paper electrophoresis—A clinical laboratory procedure:—While the present filter paper electrophoretic apparatuses are more simplified, they should be more available for routine laboratory procedures. It must be stressed that this should not take precedence over the clinical history and examination of the patient. It must be only utilized as an aid for the physician's clinical findings. Methods must be employed allowing a much better basis of comparison between different findings in laboratories[28]. There should be a standard technic or at least standardized technics within a field of application. It is not feasible to reduce all data reported in the literature to the same basis[29], since some workers express their results as ratios of a given protein component to the albumin fraction, or rela-

tive percentage concentration, as the authors utilized. Others report in terms of absolute values—that is, absolute percentage concentration. This necessitated additional chemical determination of the total protein concentration. Considerations for the extra financial expenditure and the extra time consumed for the determinations are important today. It is most essential to obtain "normal" values before one may assume that the results fall within the normal or abnormal range. This would entail the need for the adoption of a uniform method of reporting electrophoretic data in order to present a proper comparison of the results in various laboratories.

It was felt that our present technic described was most suitable for our laboratory procedure, with the least amount of experimental error, time-saving, simplicity, and inexpensiveness.

Summary and Conclusions

1. Serum protein distribution in patients with liver disease was determined by paper electrophoresis.

2. Technic of the above procedures, technical problems to prevent errors and to attain a standardized method were discussed.

3. Chemical determinations for protein fractionation, serum lipid partitions and liver tests were performed.

4. The object of the study was to evaluate further the significance of the plasma antihrombin titer level, as a clinical liver test and ascertaining its action or property by the paper electrophoretic procedure.

5. Plasma antithrombin formation is linked in liver function and it may diminish in progressively severe stages of liver impairment.

6. The plasma antithrombin titer level showed an abnormal response in 62 per cent of the liver cases, while the serum gamma globulin component was elevated in 78.6 per cent.

7. There was no real discrimination and no definite relationship between the plasma antithrombin titer levels and the serum gamma globulin changes.

8. The above comparison does not reveal the chemical significance of such a test, since the *antithrombin titer* is to be used as an *index of severity in liver diseases.*

9. There is a direct quantitative relationship between plasma antithrombin and plasma trypsin.

10. The above is a phenomenon of an intravascular physiologic complex based upon an "*antithrombinogen trypsin interaction*".

11. The *paper electrophoresis contrasted to the chemical method gave a more accurate protein fractionation and a better understanding of the disturbed physiology and underlying pathology in the patients with liver disease.*

12. The statistical significance of the various serum protein components was obtained from the "t-test", with the 5 per cent level considered of only borderline significance.

13. The *albumin showed 85 per cent below* and the *gamma component 75 per cent above normal* values.

14. A two-way frequency distribution showed a *moderate relationship between albumin and gamma components.*

15. *High gamma and low albumin levels* in the protein fraction appeared to be the best indication of abnormality for the liver patients.

16. There were *no consistent changes in the alpha-1 and alpha-2* components with varying albumin and gamma groups. The *beta globulin was not increased* in most cases.

17. The *A/G ratio was very low* when compared to normals. The changes were probably due to the fact that this is dependent on the albumin level primarily and parallels the means for the albumin.

18. Serum lipid partitions varied, depending upon the presence and intensity of the jaundice.

19. The chemical determinations of the protein fractions showed the total protein to be increased with the gamma level, but no clear-cut relationship existed for the albumin levels.

20. *Filter paper electrophoresis should be a procedure in the clinical laboratory because of its aid to the clinician.*

21. This procedure should not supplant the clinical history and physical examination.

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PNEUMOPERITONEUM AFTER GASTROSCOPY

CLAYTON K. STROUP, M.D., F.A.C.G.

and

DONALD K. PINE, M.D.

Flint, Mich.

Pneumoperitoneum following gastroscopy has been distinguished by its innocuous course and a perforation small enough to escape detection at laparotomy. This is an unusual lesion and its management is unlike that of other perforations of the stomach. Because the previous reports are incomplete, a review of the problem appears warranted in conjunction with the report of the twentieth case.

Following introduction of the flexible gastroscope in 1932, injuries to the esophagus and pharynx that were associated with the old rigid instrument were nearly eliminated. Actual passage of the instrument compares in ease with the hollow lumen gastric aspiration tube. A new hazard, however, not reported with the rigid tube, was recognized when five years after the introduction of his gastroscope, Schindler[1] reported five perforations of the stomach. In 1940[2] he added three additional cases from a survey of 22,351 gastroscopies. Five of these patients were operated upon and all had rents in the stomach wall. Three patients were treated conservatively and all made uneventful recoveries. In five instances reported by Schindler, the perforation was attributed to the Henning sponge rubber tip. This material tends to adhere to the mucosa rather than slide over it, allowing any undue pressure to force the less pliable portion of the gastroscope through the stomach wall. With the adoption of the solid rubber finger-tip, actual tears of the stomach apparently do not occur. Except for the five cases reported by Schindler of gross tears, the perforations following gastroscopy have been distinguished by the inability of any observers to locate the site. One perforation was fatal, as related by Schiff[4] at the meeting of the American Gastroenterological Association in 1942.

Of the 12 cases subsequent to Schindler's report, seven were submitted to laparotomy and four were treated conservatively. Unfortunately the mode of treatment was not recorded in the one fatal case out of the 12. In none of the operated patients was a perforation demonstrated despite instillation of methylene blue, water and oxygen under pressure. Lichstein and Wharton[9] visualized a rent in the wall during gastroscopy but were unable to locate it at celiotomy. In the three patients followed to surgery by Schindler, all with gastric carcinoma, the perforations were located on the posterior wall immediately below the cardia in two and on the greater curvature in one.

Various tentative explanations have been offered for the inability of the surgeon to find the perforation. Schindler[5] proposed that in these instances the

perforations had sealed spontaneously. Chamberlin[7] favors the explanation that the air diffused through the thin base of an ulcer and then along the lymphatics, including the perineural channels. Fierst[11] further elaborated this concept to include the perivascular spaces as pathways for the air with the development in some instances of emphysematous blebs on the serosa.

Rappaport and Finkel[13] observed their first perforation after 3,000 gastroscopies, while Schiff had two in 1,000 examinations. With the solid rubber tip gastroscope, Schindler[1] had his first perforation after 4,700 gastroscopies. The report of Myhre and Wilson[15] suggests that some leakage of air into the wall of the stomach occurs more frequently than has been thought. In 119 patients with roentgenogram 24 hours after gastroscopy, there were findings in two compatible with interstitial emphysema of the stomach.

Those situations which might favor a traumatic perforation, such as, esophageal disease, gross deformities of the spine, advanced mediastinal disease, corrosive or phlegmonous gastritis and peritonitis were not present in any of the patients.

Rupture of the stomach during gastroscopy should be suspected if the stomach fails to distend upon inflation. Abdominal distress, shoulder pain and most important, tympanitic abdominal distention which the patient cannot relieve by eructation may develop; their severity is dependent on the amount of air instilled. In a number of the milder cases the patient offered no complaint and the pneumoperitoneum was discovered incidentally on x-ray examination. Ordinarily, confirmation of the diagnosis by x-ray is simple. If the perforation does not extend through the serosa for some distance from the original site, emphysema of the stomach wall, parietal peritoneum, mediastinum and even the subcutaneous tissue may ensue. Differentiation from rupture of esophagus is usually obvious since its perforation results in catastrophic collapse, rapidly progressing mediastinitis and hydropneumothorax. In the 1940[2] survey there was one fatal rupture of the esophagus with the flexible gastroscope.

In the case being reported below, the perforation was not visible but the pathologist obtained sections through a hemorrhagic tract between the muscle layers with congestion and acute inflammation of the overlying serosa which was compatible with a perforation site. Since this patient did have an ulcerated gastric carcinoma, the mechanism may differ from that occurring in the normal stomach.

Case Report

A 69-year old white, Bulgarian, retired roofer was admitted to Hurley Hospital through the emergency room complaining of weakness so extreme that "his knees buckled under him". In addition, he had lost 20 pounds during the previous six months and for three days prior to admission he had noted swelling of

his feet. The patient denied all forms of blood loss and except for some anorexia had no gastrointestinal complaints. The patient was an asthenic, pallid, elderly man who appeared chronically ill. The skin and mucous membranes were remarkably pale. There was present a soft, blowing systolic murmur, best heard over the apex of an apparently normal size heart. The liver was felt three centimeters below the right costal margin and palpation caused discomfort. There

Fig. 1–Photomicrograph of stomach showing recent hemorrhage at site of perforation caused by gastroscope.

were no other organs or masses palpable in a scaphoid abdomen. Up to the mid leg there was present moderate pitting edema.

A marked anemia with a hemoglobin of 3.0 gm. and a red blood count of 1,670,000 was found. The bone marrow appeared normal. Under fluoroscopy the stomach appeared freely pliable, however, there was a minute projection of barium seen on the lesser curvature of the media without an associated filling defect, thought to represent a healed ulcer or an adhesion.

Gastroscopy was done without difficulty in this cooperative individual. A number of large blood vessels were seen in addition to some fresh blood within the lumen. On the lesser curvature and anterior wall there was a lobular submucosal mass which was thought to represent a neoplasm. On the day following gastroscopy the patient offered no complaints and was sent to the x-ray department for a repeat upper gastrointestinal series. A scout film taken preliminary to this examination revealed free air in the peritoneal cavity. At exploration, a thorough examination failed to reveal the site of origin of the pneumoperitoneum. The mass described at gastroscopy, measuring six centimeters in diameter, was found on the lesser curvature and posterior wall. Although the lesion extended to the serosa, there was no apparent involvement of contiguous structures and no lymph nodes were palpable. A 90 per cent gastric resection was made with *en bloc* removal of the spleen, greater omentum and tissue about the left gastric branch of the coeliac artery. The patient made an uneventful postoperative recovery and was discharged tolerating the dietary regimen surprisingly well.

Pathological examination of the stomach, measuring 20 cm. on the greater curvature and 12 cm. on the lesser curvature, disclosed a neoplastic mass 5 cm. in diameter extending to the serosa. Immediately proximal to the tumor was a hemorrhagic area with dullness and granularity of the serosa compatible with perforation. Microscopic sections showed neoplastic glandular elements penetrating the entire thickness of the stomach wall. Both the distal and proximal margins were free of tumor. Of 12 lymph nodes examined only one revealed mestastatic tumor. A section through the area of suspected perforation showed separation of the muscular layers with hemorrhage and in the overlying serosa an acute inflammatory infiltration.

Pneumoperitoneum following gastroscopy is a relatively rare occurrence. This case brings the total reported since introduction of the Wolf-Schindler gastroscope to 20 over a period of 24 years. There is apparently a distinct difference in the size and type of perforation since the introduction of the solid rubber fingertip in 1932. Prior to this time, the sponge rubber tip was associated with gross tears of the stomach which were amenable to surgical repair. We think that the perforation is too small to find at operation and apparently seals spontaneously when made with the new instrument. It is interesting that even with the old instrument, three patients with perforations recovered without operation. In 11 subsequent cases the patient had either a minute perforation which escaped detection at laparotomy (seven patients) or recovered spontaneously without surgery. This benign course is probably due to two factors. First, the perforation must be quite small since it has uniformly escaped discovery and probably seals rapidly since even the instillation of various substances into the stomach failed to demonstrate a leak. Secondly, the absence of food from the stomach in the patient prepared for gastroscopy is probably the factor responsible for the ab-

sence of peritonitis. This has been substantiated by Wangensteen[14] who induced perforations in dogs. In those animals with full stomachs the mortality was 86.7 per cent and in those with empty stomachs 6.9 per cent.

Following an unproductive laparotomy for pneumoperitoneum after gastroscopy, Chamberlin[7] advocated conservative treatment for these patients. From a similar position of hindsight, we join his advocacy of the nonoperative management of the patient with a postgastroscopy perforation. Nelson[12], Rappaport and Finkel[13] managed the large pneumoperitoneum with aspiration of the air to relieve discomfort and embarrassment of respiration. Close observation of the patient is mandatory with this regimen.

Conclusions

1. The 20th case of pneumoperitoneum following gastroscopy is recorded. It is unique in being the second case in which a gastric resection was carried out for co-existing disease and the first occasion when the possible site of perforation was demonstrated pathologically.

2. These cases are divided into two eras, those before the introduction of the smooth rubber tip in which there was a gross tear in the stomach wall and the 11 subsequent cases where the perforation escaped visualization.

3. Pneumoperitoneum following gastroscopy is usually a benign self-limited state. In view of the favorable response to medical treatment and since there has been a uniform inability to demonstrate the perforation, the authors join in urging the conservative management of these patients with the avoidance of unproductive operations.

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OBSERVATIONS ON PERFORATION AT GASTROSCOPY

Review of the Literature and Report on a Case Without Visible Perforation

R. M. FLASDICK, M.D.

and

H. D. BENNETT, M.D.

Houston, Texas

Since the advent of the flexible gastroscope, gastrointestinal perforations have been so relatively rare that no one gastroscopist sees more than a few in the course of his career. When perforations do occur, the physician and surgeon are thus faced with a relatively new situation as to what form of therapy should be instituted. This review and report are undertaken in hope to further clarify this situation.

Case report:—B. D., a 61-year old colored male, was admitted to the Veterans Administration Hospital, Houston, Texas on 14 May 1956 for investigation of right upper quadrant and midabdominal cramping pains, which had been present intermittently for 4-5 years. There had been no hematemesis, melena, diarrhea or constipation, but the patient had lost 30 pounds—from 145 pounds to 115 pounds in the previous two years. The above described pains were unrelated to meals and were relieved only by liquid medication, of unknown type.

Positive physical findings were limited to the abdomen where the liver was palpable 1 cm. below the right costal margin and slightly tender. There was mild, deep tenderness in the epigastrium. No masses were felt and no other organs were palpable.

The red cell count, white cell count and differential white cell count as well as liver function tests were within normal limits. Gastric analysis revealed 38 mEq. of free hydrochloric acid with histamine. Stool examinations were negative for ova, parasites and occult blood. X-rays of the upper gastrointestinal tract revealed the esophagus to be normal. The stomach, however, showed narrowing of the distal antral portion for a distance of a few centimeters. This was interpreted as spasm, secondary to ulcer, or perhaps infiltrating neoplasm. A repeat upper gastrointestinal series four days later revealed coarsening of the mucosal pattern and an increase in the antral tone of the stomach. Emptying, however, occurred completely in 30 minutes.

On 25 May 1956 at 8:00 a.m., using as premedication atropine, 0.6 mg., and Demerol, 50 mg., gastroscopy was performed. Local anesthesia was obtained with 2 per cent pontocaine. The flexible gastroscope was introduced with ease

Medical Department, Baylor University College of Medicine and Medical Service, Veterans Administration Hospital, Houston, Texas.

and visualization of the stomach was initially excellent. Hypertrophic mucosal folds with a gray appearance were noted on the greater curvature, and areas on the anterior wall suggested patchy atrophic gastritis. Slight nodularity was noted in these areas. No peristalsis was seen to go through the antrum. During the course of the procedure the stomach collapsed and, although it could be reinflated, adequate visualization was no longer possible. Marked belching was present at this time and it was felt the collapse was due to eructation of air. The patient complained of soreness in his right upper quadrant and abdominal distention but had no other complaints. Nothing was permitted by mouth, and during the afternoon abdominal distention persisted. Vital signs remained nor-

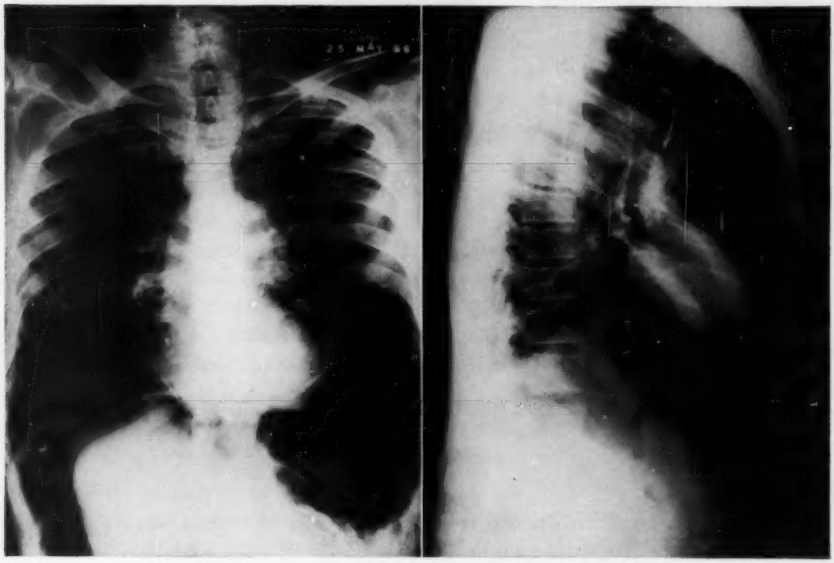

Fig. 1 Fig. 2

Figs. 1 and 2—Posteroanterior and lateral roentgenograms of chest demonstrating pneumoperitoneum, pneumomediastinum and supraclavicular subcutaneous emphysema. Lipiodol is seen in the esophagus, stomach and medial basilar segment bronchus.

mal. A Levin tube was passed into the stomach and suction applied. One hundred cubic centimeters of coffee ground material which was guaiac positive for occult blood was obtained. Bowel sounds remained normal and the abdomen, while distended, was not rigid or particularly tender. During the afternoon crepitation was palpated in both supraclavicular fossae. At 4:00 p.m. roentgenograms of the chest and abdomen revealed elevation of both domes of the diaphragm with considerable subdiaphragmatic air. Mediastinal emphysema was present, and subcutaneous emphysema was noted in the supraclavicular areas. The lung fields were clear. X-ray of the esophagus after a Lipiodol swallow

showed opaque medium in the esophagus. Droplets of the dye were present in the trachea, presumably due to aspiration, and several small drops were projected over the right cardiac border. This suggested to the roentgenologists drainage of Lipiodol through a perforation somewhere in the supradiaphragmatic portion of the esophagus, probably in the lower esophageal region (Figs. 1 and 2). White cell count at that time was 20,350 with 89 per cent neutrophils, 10 per cent lymphocytes and 1 per cent monocytes. Hemoglobin was 16.3 gm. The patient was started on penicillin and streptomycin. Further aspiration of the stomach failed to reveal additional blood.

At 11:00 p.m. surgery was undertaken with a preoperative diagnosis of perforation of the esophagus, secondary to gastroscopy. The left chest was entered through the eighth intercostal space and the mediastinum widely opened. No evidence of contaminaion of the mediastinum was noted, and no perforation of the esophagus was seen. The diaphragm was then incised radially, preserving the esophageal hiatus, and the stomach was pulled into the chest and examined. No site of perforation in the stomach could be found. A cord ligature was placed around the lower end of the esophagus and about the upper end of the esophagus with a rubber tube within the esophageal lumen. The ligatures were drawn snug; air was forced into the esophagus under pressure. The esophagus became grossly distended but no leak was ascertainable. Sterile saline was poured into the mediastinum completely covering the esophagus, but no bubbles could be seen. The ligatures were released, and the tube was passed down the esophagus into the stomach. The lower esophageal ligature was tightened and a ligature was placed around the pyloric end of the stomach. Inflation was repeated under saline, and again no loss of air could be detected. The stomach wall appeared normal throughout. The patient's chest was closed after repair of the diaphragm, and a chest catheter was brought out through the posterior axillary line, after the left lung had been completely inflated.

Initial recovery was satisfactory; however, for four days postoperatively the patient ran a temperature of 100 to 101 degrees F. and was unable to cough up secretions adequately. On 28 May 1956 bronchoscopy was performed and the tracheobronchial tree cleared by suction. A tracheotomy was performed and the patient became afebrile. Subsequently, a wound dehiscence in the thoracic incision with secondary infection occurred. Following further antibiotic therapy, a secondary closure was performed without difficulty. Repeat x-rays revealed clearing of the left costophrenic angle, and barium swallow failed to reveal abnormalities of the stomach, esophagus or duodenum. The patient had no further difficulties and was discharged 17 July 1956, a little over two months after admission.

Comment

First, as to the course of events in the present patient, it was felt that gastroscopic perforation was undoubtedly present. The information obtained from

Lipiodol swallow, namely, the presence of Lipiodol in the chest outside of the normal course of the esophagus, and the presence of mediastinal emphysema and subcutaneous emphysema made us feel that we dealt with a perforation perhaps of the esophagealcardiac junction. Based on the assumption that such perforations should be treated surgically, surgical intervention was carried out with the resultant negative findings for perforation of the gastrointestinal tract. While penetration of the gastrointestinal tract no doubt occurred, it obviously led to no persistent hole requiring surgical repair.

The incidence of perforation of the gastrointestinal tract at gastroscopy is difficult to determine. In our own case, this is the first such perforation in 151 gastroscopies. Rickstein and Horton reported their incidence as less than 1 in 3,000. In the total available literature there were found reports on 27 cases from 1936 to 1955.

In the early days of gastroscopy with use of the rigid gastroscope, perforations at the esophagogastric junction were the most frequent sites. Employing the 11 operative cases found in the literature, the following sites of perforation are noted with the flexible gastroscope: esophagus 2, gastric wall 2, jejunum 1, and in all remaining cases, namely 6, the site of perforation could not be proven. If, instead of using proven cases, all presumptions of site on the part of authors are taken into account, then site of perforation was: gastric 12, jejunum 1, and esophagus 2. It must be seen that the stomach remains by far the major site of gastric perforation at gastroscopy with the flexible gastroscope.

Part of our misjudgment as to the site of rupture preoperatively was based on the location of air. It is therefore of interest to attempt to roughly analyze the location of the air as stated by authors, and the corresponding location of the site of perforation. First, as to location of the air, in 22 cases it was present in the peritoneum, in 3 the mediastinum, in 1 the chest cavity, i.e., pneumothorax, and in 4 subcutaneously. Of these 4, in one the site was not stated, one was in the scrotum, and 2 were in the cervical area. It will be noted that this number exceeds the number of cases. This, of course, is because more than one site of air is possible in a given patient. Nevertheless, it will be noted that pneumoperitoneum was present in the vast majority.

In order to analyze the site of perforation versus the location of air, only surgically explored cases will be discussed. In the available literature 11 cases were explored surgically. Of these, as noted above, no proven site of perforation was present in 6 patients. One patient had perforation of the jejunum, 2 of the stomach, and 2 of the esophagus. It is to be understood that the cases now listed are those which list both the site of gas and the site of perforation during exploration. Of the 6 cases explored and no perforation found, 5 had air solely in the peritoneum, and 1 in the peritoneum and scrotum. These were all presumed by the authors to have represented perforations of the gastric wall or leak of air

through the gastric wall. The case with perforation of the jejunum had pneumoperitoneum. In the 2 cases with perforation of the stomach which were proven, pneumoperitoneum was present in 1 and, as in our patient, pneumoperitoneum, pneumomediastinum, and subcutaneous emphysema of the neck in the other. In the perforations of the esophagus, 1 patient had subcutaneous emphysema, presumably in the cervical area, and 1 had only pneumoperitoneum recorded. It seems that the site of air as found preoperatively might suggest one type or the other of perforation, but pneumomediastinum and cervical emphysema occurred in gastric perforations as did pneumoperitoneum in the esophageal perforation.

It is interesting in reviewing the literature to note the very definite change in the form of treatment given patients with presumed perforations of the gastrointestinal tract, following gastroscopy. This change is apparently well-founded as will be discussed below; however, it is to be noted that prior to 1948 surgery was the predominant method of choice, and since 1948 conservative therapy has reigned. In reviewing the literature 23 case reports are available where the form of therapy can be definitely ascertained. Prior to 1948, 5 cases received conservative therapy and 11 patients were operated on. Since 1948, 6 patients have received conservative therapy and only 1 patient has been operated on. This seems to represent a definite trend. It is impossible to really determine the results of treatment one way or the other. There happened to have been 11 patients in the literature and 11 treated surgically, where the results can be definitely ascertained. All patients treated conservatively have recovered. There was one death in the surgically treated patients. This, of course, has no significance except to point out the general benignity of the process as a whole.

The question arises as to why gastroscopic perforation is so reltaively benign, as compared with perforation due to peptic ulcer, traumatic rupture of the abdominal viscera, etc. As to the cause of the benignity of the perforation, two main facts stand out. First is the very fact that the site of perforation is not found so frequently at surgery. This implies that the perforation is not of the direct type but rather probably represents dissection along the layers of the gastric wall from a superficial erosion in the gastric mucosa. The pressure of air at gastroscopy, which probably exceeds normal pressures, dissects along the layers and finally ruptures into the peritoneum, mediastinum, etc. This air would be filtered through tissues and presumably almost as free of bacterial and chemical contaminant as is the air given in therapeutic pneumoperitoneum. The second factor as to benignity is probably the fact that these patients' stomachs are uniformly in fasting states and are aspirated prior to the introduction of the gastroscope. The stomach is thus empty. Work done on dogs by Byrd, Bowers, and Wangensteen has demonstrated that openings in the normal stomach which is empty seal themselves soon after perforation with leakage occurring for only a short time. They carried out perforation of the stomach in 29 fasting animals. Hold in mind these are through-and-through perforations; they are not the leak-

age type we were referring to above. When the stomachs were fasting the mortality rate was 6.9 per cent. On the other hand, if the stomach contained food the mortality rate rose to 86.7 per cent. This, of course, was without therapy of any sort. In summary, as to etiology and benignity of this conditon, the etiology is apparently twofold; approximately half have come from direct perforations and the other half presumably from leakage of air through the gastric wall, probably by a devious route. In addition, the stomachs of these patients are empty and therefore contamination of the peritoneum by chemicals and bacteria does not occur. The final factor permitting conservative therapy apparently is the advent of antibiotics, as this prevents minor contamination of peritoneal and mediastinal structures without severe infections. The fact that traumatic perforations in normal organs heal themselves very rapidly prevents additional contamination in those cases where through-and-through perforation is found.

From the above discussion it can be seen that conservative therapy is currently considered the treatment of choice in gastroscopically induced perforations. The location of air should apparently not particularly influence this choice. The swallowing of Lipiodol, while quite clever, can apparently confuse one, as Lipiodol may be gotten into the lungs directly through the bronchial tree and then be suspected to have arrived there by way of the intestinal tract.

Summary

A case of pneumoperitoneum, pneumomediastinum, and subcutaneous cervical emphysema following gastroscopy is reported. No site of perforation could be demonstrated at surgery even with drastic measures. Therapy of such perforations is discussed and the conservative approach strongly recommended unless true signs of localizing infections are demonstrated.

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DUODENOCOLIC FISTULA AS A COMPLICATION OF PEPTIC ULCER

LEON SASSON, M.D., F.A.C.G.*

and

SAMUEL WEISKOPF, M.D.†

Bronx, N. Y.

Benign duodenocolic fistula is a rare lesion. Most cases of fistula between the colon and duodenum are due to carcinoma of the large bowel. Up to the present, only 16 cases of benign duodenocolic fistulas have been reported, and of these only 6 have been due to a perforated peptic ulcer. The purpose of this paper is to present a seventh case of duodenocolic fistula due to peptic ulcer and to discuss its clinical features and pathogenesis.

Review of the Literature

In 1940 McPeak[1] reported 2 cases in which each patient had a fistula between the duodenum and the transverse colon on the basis of a perforated duodenal ulcer. In one case the fistula involved the first portion of the duodenum and in the other it involved the junction of the second and third portions. One survived surgery.

In 1944 McClinton[2] reported a case in which a 44-year old man had a duodenal ulcer for many years and had an attack suggesting perforation two years previously. Following this, he developed a continual diarrhea and at operation a fistula was found 2½ inches from the pylorus between the duodenum and the transverse colon. He recovered following surgery.

In 1948 Rialton[3] reported a case of a 45-year old female who had a 7-year history of epigastric distress with a recent exacerbation of almost constant pain radiating to the back and vomiting. There was no diarrhea but there was weight loss. Gastrointestinal series showed a duodenal ulcer with a perforation pocket and a fistula to the transverse colon. At laparotomy a mass, the size of a hen's egg, was attached to the bulb and transverse colon. It was left undisturbed and a Devine partial gastric exclusion operation was done. Postoperatively a marginal ulcer developed and she was reoperated and a vagotomy was done. The mass seen at the first laparotomy had disappeared. The patient made a successful recovery.

In 1951 Rife[4] reported a case of a 45-year old man with a 4-year history of intermittent diarrhea and a weight loss of 50 lbs. with no previous ulcer type

From the Diagnostic Clinic of Lebanon Hospital, Bronx, N. Y.

*Chief of Gastrointestinal Out Patient Department and Adjunct Physician, Lebanon Hospital, Bronx, N. Y.

†Director, Out Patient Medical Department and Attending in Medicine and Gastroenterology, Lebanon Hospital, Bronx, N. Y.

history. Gastrointestinal series revealed a deformed bulb and a duodenocolic fistula. At operation a fistula between the second portion of the duodenum and the transverse colon was found which was interpreted as being due to a perforated duodenal ulcer of the second portion of the duodenum. Recovery was complete after operation.

In 1956 Nash and Daland[5] reported the sixth case of duodenocolic fistula secondary to peptic ulceration of the duodenum. The patient was a 39-year old

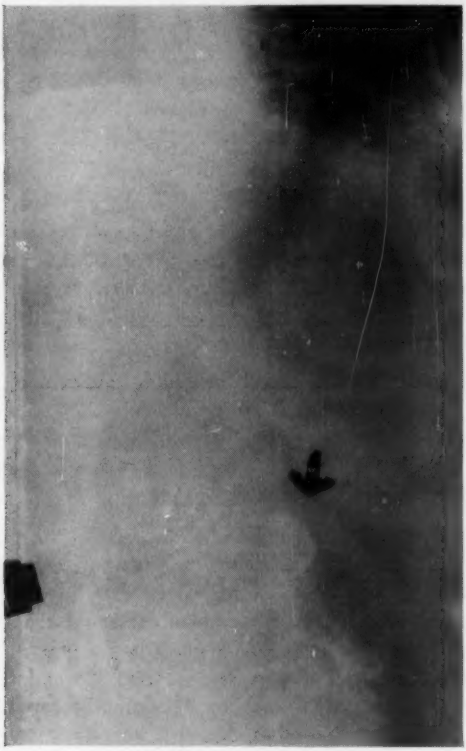

Fig. 1—Gastrointestinal series showing distortion of antrum and bulb.

male who had a 2-year history of duodenal ulcer with a recent exacerbation of pain and a 20 lb. weight loss. On examination there was tenderness and rigidity in the right upper quadrant with a palpable mass. Gastrointestinal series showed a prepyloric defect and obstruction of the second portion of the duodenum. Barium enema showed a filling-defect of the hepatic flexure. This was interpreted as an extrinsic mass associated with the stomach, duodenum and colon probably secondary to a perforation of a malignant tumor involving the distal portion of

the stomach. At laparotomy a mass was found involving the distal end of the stomach, duodenum and hepatic flexure and extending under the liver. Dissection disclosed a fistula between the second portion of the duodenum and the hepatic flexure and an abscess under the left lobe of the liver. The duodenal perforation was closed and a gastrojejunostomy and segmental resection with end-to-end anastomosis of the colon was done. Postoperatively a jejunal ulcer formed but the patient failed to return for further study.

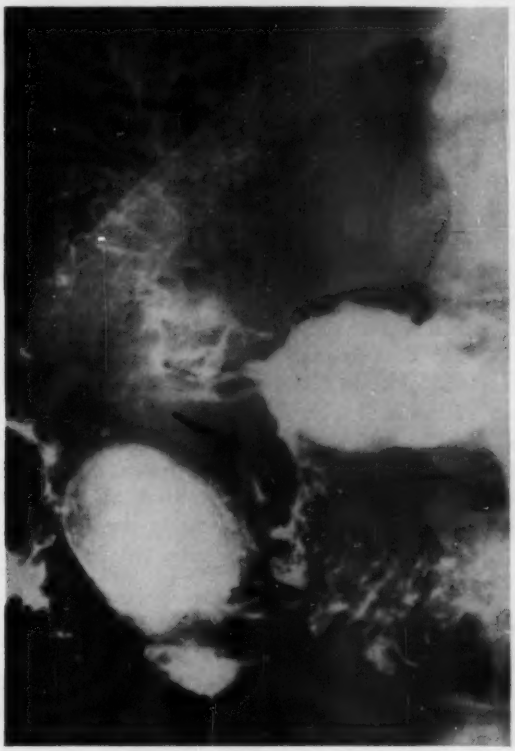

Fig. 2—Postevacuation film of barium enema showing fistula between transverse colon and pool of barium in the area of the antrum and bulb with retrograde filling of the stomach with barium.

Ten other cases of benign duodenocolic fistula due to causes other than peptic ulcer have been reported in the literature. In 1933 Rees[6] reported a case due to perforation of a typhoid ulcer. In 1935 Ormandy and Bargen[7] reported a case due to thromboulcerative colitis. In 1939 Ogilvie[8] reported two cases due to caseating tubercular lymph nodes. In 1939 Krock[9] reported a case he believed to be due to a perforated duodenal diverticulum. In 1947 Lovell[10] reported two

cases due to ulcerative colitis. In 1951 Winfield[12] reported a case due to either tuberculous lymphadenitis or a nonspecific lesion with abscess and fistula formation. In 1954 Neville[13] reported a case secondary to acute cholecystitis.

Report of a Case

This case represents the 17th case of a benign duodenocolic fistula to be reported and the 7th case of fistula complicating peptic ulcer.

C. S. was a 53-year old white male who was admitted to the Diagnostic Clinic of Lebanon Hospital on 5 April 1955 because of a history of hematemesis and melena 13 years ago, followed by recurring episodes each spring and fall of intermittent periumbilical pain, relieved by food and antacids. He had a past history of alcoholism and smoked 20 cigarettes daily. Examination revealed a well developed man weighing 177 lbs. with clubbed fingers, emphysematous chest, and occasional rhonchi bilaterally. Abdominal examination was negative.

Hgb. was 15 gm. with 4.9 million R.B.C. and a normal W.B.C. and differential count. Stool was positive for occult blood. Wassermann was negative. Blood urea nitrogen, proteins, thymol turbidity, and cephalin flocculation were normal. Glucose tolerance test showed a diabetic-type curve and there was 2 plus sugar in the urine. Gastric analysis after histamine showed free acid of 30 to 100 units and a total of 40 to 110 units. Gastrointestinal series showed a persistent irregularity of the bulb with a fleck of barium in the region of the bulb in the 6 hr. film. There was also a distortion of the contour and configuration of the antrum (Fig. 1). This was interpreted as representing a duodenal ulcer with suggestion of probable adhesions around the antrum. A clinical and radiological diagnosis of mild bullous emphysema of the lungs was also made.

Ten days after his admission to our clinic, work-up had to be discontinued because he developed severe, constant, epigastric pain which lasted for several days and he had to be treated with antacids and bedrest. One week later he developed diarrhea which continued daily for 2½ months, after which time he returned to our clinic for further study. During this time he had a weight loss of 30 lbs., and complained of diarrhea seven times daily consisting of about 4 stools every morning and 3 stools every evening, with no pain and no blood or mucus in the stool. Barium enema, repeated twice, showed the cecum to be high in position and demonstrated barium appearing within the stomach (Fig. 2). A diagnosis of fistula between colon and stomach or duodenum was made and the patient was admitted to the Surgical Service of Lebanon Hospital. His Hgb. at that time was 17.4 gm., his total protein 8.0 per cent, albumin 3.7 per cent and globulin 3.4 per cent.

On 26 July 1955 a laparotomy was done and the prepyloric area of the stomach was found to be involved in a mass of inflammatory tissue which was not hard and which did not show evidence of malignancy. Division of the fistulous

tract left an opening in the proximal third of the transverse colon below and a double barreled opening above, one extending into the prepyloric area of the stomach and the other entering into the beginning of the second portion of the duodenum. The opening in the colon was sutured, and the double barreled openings were closed in continuity, thus forming a gastroduodenostomy. A vagotomy was also done. Two Penrose drains were placed in the right gutter and brought out through a stab wound to the right of the incision. On the fifth postoperative day, it was observed that there was profuse drainage of bile through the drains, and by the tenth day he was losing about 4 liters of fluid from the drain site, and had developed a hypochloremic alkalosis despite replacement therapy. A Witzel jejunostomy was done under local anesthesia, and postoperatively the drainage fluid plus jejunostomy feedings were fed into the stoma. Three days later under general anesthesia, the patient's abdomen was reopened, and it was found that the previous gastroduodenal anastomosis had separated. A subtotal gastrectomy with a Hofmeister type gastrojejunostomy was performed. The duodenal stump was left open and a duodenostomy tube was used for closure. Pathology of a resected portion of the stomach with first portion of the duodenum attached showed nonspecific gastritis and duodenitis, with foreign body granulomata of the serosa. One week postoperatively, the duodenostomy tube was removed. He continued, however, to lose approximately 5 liters from the fistula daily and gradually developed hypoproteinemia, edema, pneumonia, and terminally icterus, and expired in coma on 13 September 1955, 36 days following the third operation.

Postmortem examination showed an open duodenal fistula, fresh peptic ulcers of the stomach and jejunum, partial breakdown of the gastrojejunal suture line with a posterior gastric abscess, chronic cholecystitis with ascending cholangitis and bile stasis of the liver, multiple areas of localized peritonitis with adhesions, and aspiration pneumonia.

Comment

This case represents the 7th reported case of perforation with fistula formation of a duodenal ulcer into the colon. Analysis of the 6 previously reported cases and the authors' case in Table I shows that 6 of the cases reported have been found in males and one in a female. The age distribution was between 39 and 58. In two cases the site of perforation was at the first portion of the duodenum; in 4 cases it was at the second portion; and in one it was at the junction of the 2nd and 3rd portions. The site of fistula formation into the colon was at the transverse colon in 5 cases and at the hepatic flexure in two. In one case (the authors') a second fistulous tract to the antrum formed. The predominant complaints were those of diarrhea from 5½ months to 4 years, weight loss of from 25 to 50 lbs., and exacerbation of ulcer pain. The onset in 3 cases was that of sudden exacerbation of the ulcer pain followed by diarrhea, in 2 cases that of diarrhea without antecedent pain, and in 2 cases that of exacerbation of pain with weight

loss but no diarrhea. In 5 cases the barium enema established the diagnosis positively; in 2 cases it was established by gastrointestinal series; and in one it may have been suggested by the finding of a confined perforation in the gastrointestinal series. Five out of 7 cases survived following surgery.

Pathologically, duodenocolic fistula complicating peptic ulcer disease is an extension of a walled-off or confined perforation of a peptic ulcer in which further penetration occurs finally perforating into an adjacent viscus forming a fistula. In our case fistulas formed in two directions, one into the transverse colon and another into the gastric antrum. Haubrich, Roth and Bockus[14] recently outlined the pathogenesis involved in confined perforations. Penetration of the ulcer occurs through the muscular wall to the serosa producing an inflammatory reaction. This may heal and scar with fibrous adhesions, or it may penetrate deeper causing necrosis and sloughing of adjacent tissues, thus forming an extra-alimentary cavity. This is seen on x-ray as an accessory pocket with barium, or gas, or both, and is clinically manifested by back pain, nocturnal distress, change in anterior pain, altered rhythm, and refractoriness to relief. They point out that the wall of the confined perforation is poorly vascularized and is easy prey to acid peptic digestion, healing slowly, and subject to repeated breakdown and reactivation. This may heal with fibrous adhesions, or may perforate into an adjacent viscus forming a fistula.

Duodenocolic fistula complicating peptic ulcer should be suspected in a patient with a history suggestive of duodenal ulcer with recent exacerbation of pain, diarrhea, and weight loss. A voracious appetite may be present[1]. Examination may reveal a mass in the right upper quadrant[5]. In x-ray studies particular attention should be paid to the second portion of the duodenum in a search for an accessory extra-alimentary pocket or a fistulous tract, since this is the area most often involved. Too much reliance, however, should not be placed on the inability to demonstrate these findings. Haubrich et al[14] reported that out of 35 cases with proven confined perforations only 20 (57.1 per cent) were seen on the preoperative x-ray films. Of the 7 cases of duodenocolic fistula discussed in this paper (Table I) only 2 showed the fistula on upper gastrointestinal series, and one other case showed a confined perforation. The diagnosis of duodenocolic fistula is usually established by barium enema showing the presence of barium in the duodenum and stomach.

Surgery should be recommended once the diagnosis is made. Prior to surgery, it is of vital importance to improve the patient's nutritional status and restore some of the weight loss. McClinton reported, in the management of his case, that he passed a Miller-Abbott tube to a point beyond the fistula and fed the patient 5,000 calories daily. The diarrhea continued, however, and he reasoned that although the food now bypassed the fistula, the HCl continued to enter the colon by means of the fistula thereby producing diarrhea. Zollinger[15] has pointed out that the administration of sulfasuxidine increases the absorption

TABLE I

Summary of Features of Cases of Duodenocolic Fistula Complicating Peptic Ulcer

Reported By	Age	Sex	History of ulcer	Duration of diarrhea	Weight loss lb.	Type of onset	Portion of duodenum involved	Portion of colon involved	Gastrointestinal series showing fistula	Barium enema showing fistula	Results with surgery
McPeak 1940	58	M	?	3 yrs.	25	Diarrhea	1st	Hepatic flexure	No	Yes	Good
McPeak 1940	46	M	15 yrs.	6 mos.	46	Severe ulcer pain, then diarrhea	2nd & 3rd	Transverse colon	No	Yes	Died
McClinton 1944	44	M	Many years	2 yrs.	30	Severe ulcer pain, then diarrhea	2nd	Transverse colon	Suggestive	Yes	Good
Rialton 1948	45	F	7 yrs.	None	?	Severe ulcer pain	1st	Transverse colon	Yes	Not done	Good
Rife 1951	45	M	No	4 yrs.	50	Diarrhea	2nd	Transverse colon	Yes	Yes	Good
Nash et al 1956	39	M	2 yrs.	None	20	Severe ulcer pain	2nd	Hepatic flexure	No	No	Good
Authors 1956	53	M	13 yrs.	2½ mos.	30	Severe ulcer pain, then diarrhea	2nd	Transverse colon	No	Yes	Died

of fat in the gastrointestinal tract from 30 per cent before the administration of sulfasuxidine to 90 per cent after its administration, and advises that this be used preoperatively. He believes that the diarrhea is due to the presence of abnormal bacterial flora in the small bowel which is there as a result of reflex of colonic contents through the fistula, and that the sulfasuxidine improves the nutritional status by destroying these bacteria.

Summary

The seventh case of duodenocolic fistula complicating peptic ulcer is reported. The clinical triad consists of chronic diarrhea, weight loss, and a history of peptic ulcer. The fistula most often involves the second portion of the duodenum and the transverse colon. A review of the literature is presented and the pathogenesis discussed. Comments are made concerning the diagnosis and treatment of this condition.

Acknowledgement

We wish to express our gratitude to Dr. B. S. Kahn of the Diagnostic Clinic and to the Surgical, Radiological, and Pathological Departments.

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RELATIONSHIP OF OBESITY AND THE HYPERSTHENIC HABITUS TO POSTBULBAR DUODENAL ULCER

IRVING K. ETTMAN, M.D.*

Memphis, Tenn.

In recent years considerable literature has accumulated on the subject of postbulbar duodenal ulcer[1,10]. For the most part, this has been concerned with clinical features of this condition, with particular emphasis on the frequency of hemorrhage, and with radiographic differential diagnosis.

Of the many unanswered questions related to this specific phase of the general problem of peptic ulcer, two will be discussed in this report: 1. When should the radiologist or clinician be particularly alert to the possibility of an ulcer distal to the duodenal cap? and 2. What factors are involved in the relatively uncommon formation of peptic ulcers in this area? It is felt that there is a relationship between these two questions and an attempt will be made to demonstrate their interdependence.

In the course of performing routine fluoroscopy and film reading, we have observed an apparently high incidence of the hypertonic type of stomach in our patients with postbulbar ulcers. A review of 33 cases reveal that all, or 100 per cent, demonstrated this type of stomach. Further investigation by physical examination in most instances, and by review of the clinical data in patients not available for clinical study, revealed that invariably these individuals were obese and stocky, and showed short broad trunks with wide costal angles and transverse hearts. In no instance in our series was there a patient of the asthenic body habitus with a typical hypotonic or J-shaped stomach.

A review of certain pertinent features of the anatomy of the duodenum is essential for the understanding of the radiographic variations of this structure as influenced by the body habitus of the patient.

Anatomy of the Duodenum

The duodenum is the first part of the small intestine, extending from the pylorus to the duodenojejunal junction[7]. Following its origin at the pylorus, the duodenum passes backwards, upwards, and to the right, varying slightly in direction according to the degree of distention of the stomach. It then makes a sharp curve, the superior duodenal flexure or *genu superius*, and descends along the right lateral margin of the pancreas to about the level of the 4th lumbar vertebra. Here it makes a second bend, the inferior duodenal flexure, and then

*Department of Radiology, Veterans Administration Hospitals (Kennedy Division), Memphis, Tenn.

passes almost horizontally from right to left across the vertebral column. The duodenum now ascends anterior to the abdominal aorta, an approximate distance of 2.5 cm., and joins the jejunum opposite the 2nd lumbar vertebra, forming the doudenojejunal flexure at the ligament of Treitz.

We are concerned at present with the first portion, or *pars superior,* extending from the pylorus to the *genu superius* referred to above. This part of the duodenum varies in size and position during fluoroscopy and roentgenographic examination and is affected by the body habitus of the individual and the type of stomach. The proximal ⅝ths of this portion comprises the duodenal cap radiographically and differs anatomically from the remaining segments of the duodenum. In the bulb, the mucous membrane does not consist of the large transverse folds, the *valvulae conniventes,* which project into the lumen of the bowel and

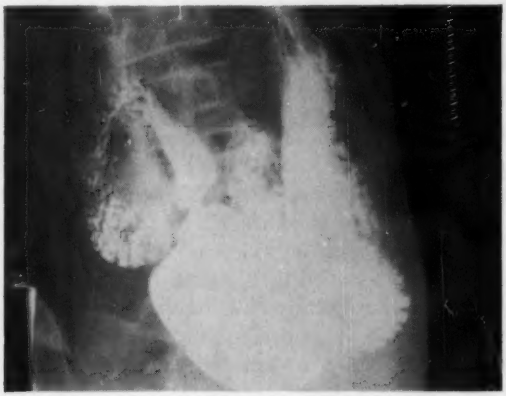

Fig. 1—Variations in the normal stomach and duodenum due to the body habitus. Hyposthenic type—Stomach is of the hypotonic type, the characteristic J-shaped stomach, duodenal bulb directed upward.

extend transversely around it. The mucous membrane of the bulb is similar to that of the stomach. The *valvulae conniventes* appear in the distal portion of the first part of the duodenum and account for the tufting feathery appearance of the duodenum just distal to the bulb.

Radiographic Appearance

Variation of the normal radiographic anatomy of the stomach and duodenum is greatly influenced by the body habitus of the subject[2,5,8]. Ordinarily, reference is made to two extremes of bodily constitution, the hyposthenic and hypersthenic. A third body habitus, the sthenic or orthosthenic is described as a less well-defined type of midway between the extremes and possessing certain

features of both. The constitutional types are: 1. hyposthenic 2. hypersthenic 3. sthenic or orthosthenic (Figs. 1 and 3)).

The hypersthenic type individual demonstrates a short, broad trunk, a short lumbar region, wide costal angle and transverse heart. On x-ray the stomach is referred to as hypertonic and the *pars media* runs obliquely from the left superiorly to the right inferiorly, so that the lower pole is often situated as much as 3 or 4 inches above the iliac crest in contradistinction to the hypotonic stomach. The antral region is narrower than the *pars media* and the angle between

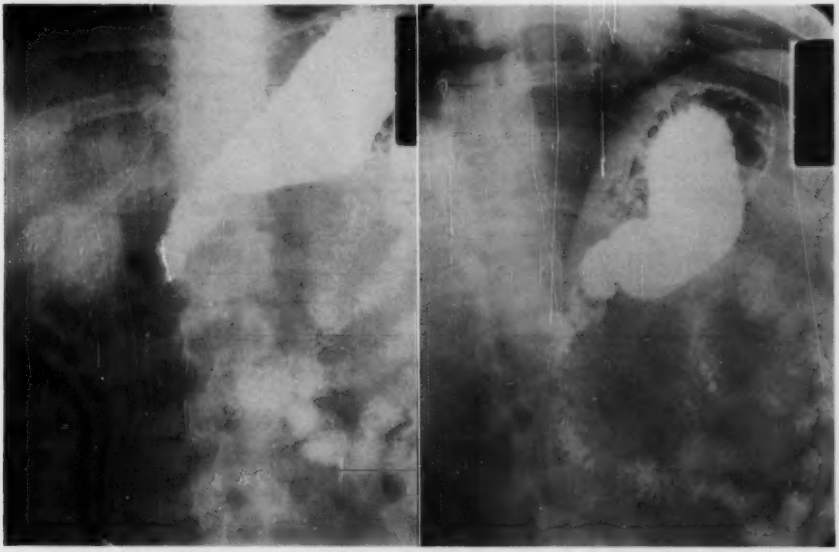

Fig. 2a Fig. 2b

Fig. 2a—Hypersthenic type individual—Stomach is of the hypertonic or "steerhorn" type. The first portion of duodenum directed downward and posteriorly.

Fig. 2b—Oblique View—Demonstrated the shortened J-shaped stomach, and opening up of the junction of first and second portion of duodenum *(genu superius)*.

the antrum and *pars media* is greater than 90°, unlike the acute angulation characteristic of a J-shaped stomach. The so-called steerhorn stomach is merely an exaggeration of the hypertonic type in which there is complete straightening of the *pars media* and the prepyloric area, with the pylorus further posterior than the *pars media*. On the oblique view, it can usually be shown to be a shortened J-shaped stomach with the pyloric end and the first part of the duodenum running posteriorly instead of to the right. This is due to the fact that the cardia and *pars media* lie in an anterior plane to that of the antrum and bulb which are in the posterior plane (Figs. 2a and 2b).

In the hypertonic type of stomach, the first part of the duodenum is horizontal or slightly oblique and is situated in the same line or plane as the pylorus. In the extreme types, as the steerhorn type, the entire bulb is projected below the level of the prepylorus. The duodenal bulb is smaller and rounded and is directed posteriorly in hypertonic or obese individuals and in the PA view, the duodenal bulb or cap is obscured by the overlying antrum. The duodenal loop appears widened and the duodenal junction lying at a lower level than the pylorus. The widening of the duodenal sweep should not be confused with a lesion in the head of the pancreas, as the sweep in cases of hypersthenic types

Fig. 3—Orthsthenic or sthenic type demonstrating an orthotonic stomach with the lower pole of stomach above the iliac crest. The duodenal bulb directed upward and to the right.

is due to the high position of the stomach, resulting in the uncovering of more of the duodenum. In our opinion, a widened duodenal sweep is a common normal finding in patients with hypertonic stomachs and obesity and is probably one of the least helpful signs of pancreatic disease.

In view of these anatomic and radiographic facts, it is clear that the roentgen examination is not complete unless the patient is examined in the extreme right anterior oblique and frequently the right lateral positions. In these views, as emphasized by Ball[3] and others, the *genu superius* and the postbulbar area

of the duodenum can best be visualized without the pylorus overlying and obscuring the duodenum (Figs. 4a and 4b).

The most frequent site of postbulbar ulceration, according to Borman[4], is in the region of the junction of the first and second portions of the duodenum on the medial border adjacent to the pancreas. The infrequency of diagnosis of ulcers distal to the first portion of the duodenum, compared to the actual incidence, may be related in part to the failure of the fluoroscopist to demonstrate this relatively inaccessible region. Features of x-ray diagnosis have been well summarized by Finkelstein[6].

As stated initially, 33 of our cases of postbulbar duodenal ulcers were noted to have hypertonic or steerhorn type of stomachs and we have not seen a case

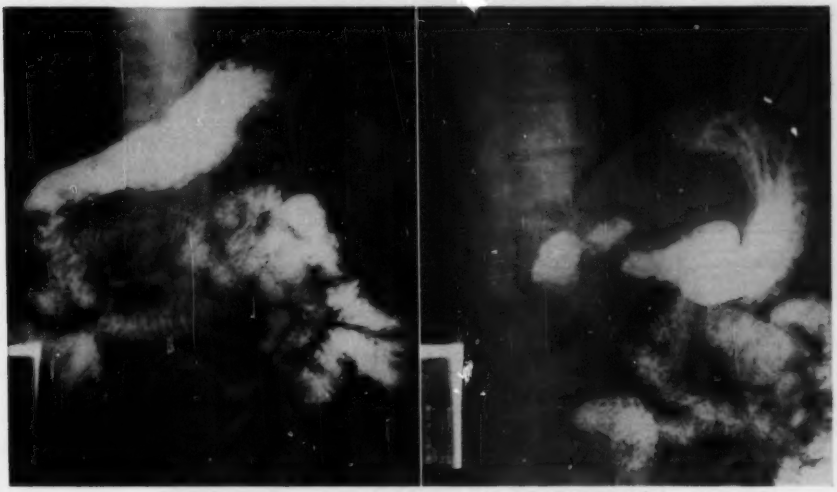

Fig. 4a Fig. 4b

Fig. 4a–Obese male, in PA view postbulbar ulcer obscured by pylorus.
Fig. 4b–Oblique view, uncovering of the duodenum revealing the crater in the postbulbar area.

in a patient with a hypotonic or J-shaped stomach. It seems rational to speculate on the possibility that purely mechanical factors are significant in the formation of postbulbar ulcer in these patients.

In the patient with the true hypotonic stomach, gastric juice is propelled through the pylorus so that it comes in contact directly with the duodenal bulb. In the hypertonic stomach, however, and particularly its exaggerated form, the corrosive juice may be squirted directly into the postbulbar area or may be held up at the *genu superius* as the duodenum bends posteriorly. This may conceivably be of significance in the formation of postbulbar ulcer in obese, stocky patients with hypertonic stomachs (Fig. 5).

Without theorizing on the pathogenesis of ulcer formation, one may state with reasonable certainty that peptic ulceration occurs only in those areas of the digestive tract which are bathed by acid peptic juice. In addition to the destructive action of gastric juice and the presence of a sensitive mucosa and the protective factors of the body, the localization of an ulcer probably bears some direct relationship to the direction of the flow of the acid chyme and its concentration in a particular area. Thus it is well known that the majority of gastric ulcers occur along the "magenstrasse" and anastamotic ulcers following

Fig. 5—Large postbulbar ulcer of duodenum verified at surgery. Laparotomy for massive uncontrollable hemorrhage. Note the hypertonic stomach and widened duodenal loop.

gastrojejunostomy are most common in the efferent loop just distal to the stoma where the stream of gastric juice attacks the jejunal mucosa most vigorously. The frequency of peptic esophagitis associated with conditions permitting of gastric reflux needs no comment. Lastly, it has been shown that ulcers in association with a Meckel's diverticulum are prone to occur distal to the heterotopic gastric mucosa and not in the gastric mucosa *per se*[9]. Ulceration is found in the ileal lining at the edge of the gastric mucosa, often at the base of the diverticulum.

Conclusions

1. In patients with postbulbar duodenal ulcer, obesity, the hypersthenic body habitus, and the hypertonic type of stomach are frequent findings, in this series of 33 cases.

2. The use of extreme right oblique and lateral positions is re-emphasized in the search for postbulbar ulcer. This is of particular clinical importance in the hypersthenic individuals with upper gastrointestinal hemorrhage of obscure origin.

3. It is stressed that a widened duodenal loop is often a normal finding in the hypersthenic patient.

4. It is postulated that mechanical factors related to the direction of the flow of acid gastric juice may be of significance in the occurrence of ulcer distal to the bulb, rather than in the bulb *per se*, in patients of the hypersthenic body habitus.

Summary

In a review of 33 cases, the presence of postbulbar duodenal ulcer was found in hypersthenic type of individuals with the hypertonic stomach.

Acknowledgment

The author wishes to express his appreciation to Dr. Michael L. Gompertz, Chief of Gastroenterology Section, for his invaluable assistance.

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UNUSUAL FINDING IN THE STOMACH DURING GASTRECTOMY FOR CANCER*

J. PROPATORIDIS, M.D., F.A.C.G.

and

X. G. YOTIS, M.D.

Athens, Greece

Cases of foreign bodies of different kinds and size found in the stomach, deliberately swallowed or because of error, have been repeatedly reported in the past. What is really unusual, however, is the accidental finding of such a

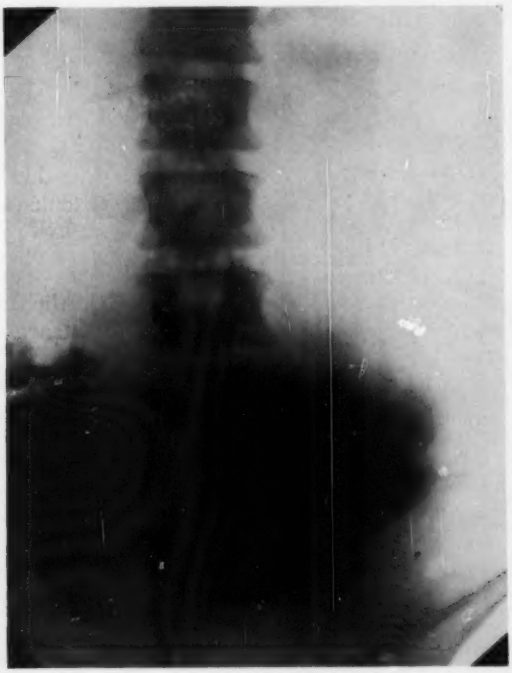

Fig. 1—Radiograph taken 48 hours after the barium meal: Most of the opaque medium still remains in the stomach.

foreign body in the stomach, long after it had been swallowed, during operations for some other cause.

*From the 2nd Surgical Clinic of the General State Hospital of Athens. Director: Jordan Propatoridis, M.D., F.A.C.G.

We believe that such a case is worth reporting, because of its extreme rarity.

Case Report

H. S., female, aged 42 years, was admitted to the 2nd Surgical Clinic of the General State Hospital of Athens on 13 February 1957, with an eight months' history of severe epigastric pain, constant day and night, associated with nausea and sometimes vomiting. During the last three months the symptoms worsened; vomiting occurred immediately after meals, thus rendering the intake of food impossible. Owing to that, the patient's general condition deteriorated rapidly, she lost weight considerably and complained of extreme weakness.

On admission the patient weighed 32 kg; she was of extreme pallor, emaciated, and almost completely dehydrated. Her abdomen was moderately distended and on palpation it revealed the existence of an irregular tumor, the

Fig. 2—The resected part of the stomach (5/6) showing the neoplastic mass of the pylorus.

size of an orange, lying in the middle right abdominal quadrant, near the umbilicus. The mass was of hard consistence, slightly movable, it caused pain on palpation and gave a dull sound on percussion. The pattern of a largely distended stomach was traced through the abdominal wall with evident peristalsis. Gastric succussion was also present.

Other symptoms:—Nothing abnormal detected. Blood pressure 90/40 mm.

Blood count:—R.B.C. 2,200,000; Hgb., 42 per cent; W.B.C. 6,000.

Blood urea:—0.27 mg./%.

Blood sugar:—0.84 mg./%.

A barium meal showed complete pyloric stenosis of an immensely distended stomach, the lower pole of which extended down to the ***symphysis pubis*** (Fig. 1).

In view of her general poor condition the patient underwent a preliminary treatment with blood tranfusions, intravenous isotonic saline and dextrose solutions, injections of the main vitamins, liver extract and other tonics. In addition, the stomach contents were lavaged daily by means of an esophageal catheter.

While under this treatment the patient continuously complained of severe epigastric pain, but, nevertheless, her general condition improved, she put on weight and nearly a fortnight after her admission she was considered fit for operation.

Under general anesthesia, the abdomen was opened through a middle epigastric incision. A hard neoplasmatic mass, the size of a man's fist, was found, involving the pyloric antrum (Fig. 2). Enlarged lymph-nodes on both curvatures of the stomach were also noted. In view of the operability of the case, a

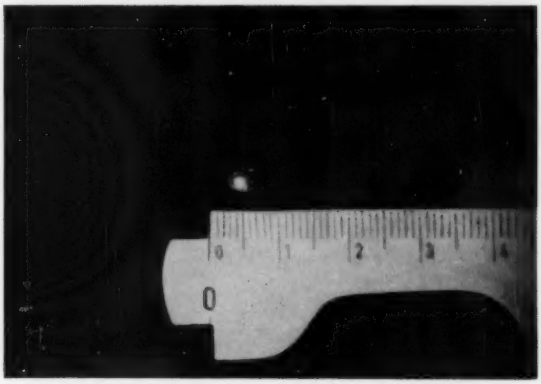

Fig. 3—The mercury found in the stomach.

radical gastrectomy was decided upon; ¾ of the stomach were resected, together with the gastrocolic ligament and the adjacent lymph-nodes. During the Polya-type gastroenterostomy and while the remaining small part of the fundus of the stomach was being wiped, minute globules of silvery brightness were noticed on the sponge. These awakened our curiosity and wiping was repeated, each time bringing out the same bright globules scattered on the surface of the gauze. One of these, the size of a lentil, was large enough to be easily identified as metallic mercury. Finally, almost all the quantity of the metal (about 5 gr.—Fig. 3) was collected in a small glass tube, a task carried out with much difficulty, owing to the great liquidation of the substance.

The operation was then completed, a nylon tube was passed down to the region of the duodenal stump for drainage and the abdomen closed in layers.

The patient made an uneventful postoperative recovery. Her wound healed at first intention. She obviously enjoyed rapid improvement of her general condition and when discharged two weeks later, she had already gained 2.5 kg.

Comment

Mercury is a shining, silver-white, volatile metal, liquid in common temperature, having a specific gravity of 13.59. The chemically pure mercury, when taken orally, displays no pharmacologic activities, because no ions of Hg^{++} are formed in the case. *(Corpora non agunt nisi soluta sive solubilia).* People, however, particularly laymen, ignore this and understand metallic mercury as a strong poison. Therefore, the first thing we thought of immediately after discovering the metal in the patient's stomach, was the possibility of her having swallowed the mercury of one of the thermometers in the clinic, in an attempt to commit suicide. We also considered the fact that she might have drunk the metal sometime before her admission, as a possible remedy against constipation, of which she complained because of her pyloric stenosis. Let it be further reminded that the intake of mercury was advised by doctors in times past, as a means to overcome acute intestinal obstruction.

Finally, we were informed by the patient herself, as soon as she awoke from the narcosis, that she had taken the small quantity of mercury we discovered in her stomach, three months ago, in her wish to overcome fear and anxiety caused by her severe illness. She stressed moreover, that people in her native village regard mercury as "an antidote against evil eye" and they get it at the grocer's, from where she herself had got it.

The literature on the subject has been reviewed and, so far as is known, no other similar case has been reported. Besides its rarity, however, the present case is of obvious interest for two main reasons also: 1. because a foreign body (i.e. mercury) was found unexpectedly during gastrectomy for cancer and 2. because three months after the oral intake of the mercury in spite of its great specific gravity, it still remained in the stomach of the patient, owing to the complete pyloric stenosis.

THERAPEUTIC EVALUATION OF SIPPYPLEX*

SAMUEL WEISS, M.D., F.A.C.G.
JEROME WEISS, M.D., F.A.C.G.
and
BERNARD WEISS, M.D.
New York, N. Y.

Introduction

To review the causes, pathology and treatment of peptic ulcer, gastritis, hyperacidity, hypersecretion, and other manifestations due to gallbladder and biliary disease seems unnecessary.

This paper will present the case histories of ten patients who are representative of the 110 that made up this series.

In all of the cases we prescribed Sippyplex† in doses of one or two teaspoonfuls several times a day, preferably between meals as well as a special "ulcer diet". Patients who were known to have allergies to milk in any form and especially to vitamins did not react favorably, and Sippyplex® had to be discontinued.

Case Reports

Case 1:—H. R. S., male, 26 years of age, single, presented himself on 4 April 1957, with a chief complaint of loss of weight for the past six months. His history dated back to 1947 at which time he bled from the gastrointestinal tract which was diagnosed, according to the patient as ulcerative colitis. He never had diarrhea, nor was a sigmoidoscopy or barium enema study performed then. Treatment consisted of Rutin® and Vitamin C and within a short period the bleeding episode cleared up.

Up to the present time, including the years 1951 to 1953 while he was in the army there were no symptoms referable to the gastrointestinal tract. Four months ago he suffered an emotional upset when the father of his fiancée, a physician, opposed the marriage because of the bleeding episode in 1947. This problem was soon followed by the appearance of rectal bleeding associated with severe heartburn.

Physical examination was essentially negative. The blood pressure was 122/80, weight 138¾ lbs. and the hemoglobin 81 per cent. A fasting gastric

*Aided by a grant from The Purdue Frederick Company, New York City.
†Sippyplex was supplied through the courtesy of The Medical Department of The Purdue Frederick Company, New York City.

analysis showed 45 units of free and 68 units total acidity. The stool was negative for occult blood. X-ray study revealed a constant deformity of the duodenum, although no definite ulcer crater was demonstrable. He was placed on a simple regimen consisting of a bland diet supplemented by Sippyplex® powder. Improvement began immediately and continued uneventfully until he was completely asymptomatic. A repeat gastric analysis two months later showed marked reduction in both free and total acidity. He was advised to continue the diet and the Sippyplex® powder without interruption. When last seen several months later, he remained symptom-free and continued to show the marked reduction in gastric acidity.

Case 2:—J. B., female, 38 years of age, single, secretary, was first seen in February, 1953, complaining of heartburn, nausea, vomiting and constipation. Her blood pressure was 130/70, weight 115½ lbs., and hemoglobin 83 per cent. A fasting gastric analysis showed 65 units of free and 82 units total acid. The stool after a meat free diet was positive for occult blood.

Fluoroscopy and roentgenography demonstrated a definite duodenal ulcer. Treatment with a bland diet, alkalis and anticholinergic medication resulted in some improvement. Any minor emotional disturbance, however, was soon followed by a prompt recurrence of all the original symptoms. At times relief could only be obtained by self-induced emesis. A more severe emotional upset resulted in severe constant abdominal pain, vomiting and a loss of weight to 93½ lbs. at which time the urine was positive for acetone and diacetic acid.

She was admitted to the hospital for a period of two weeks, where daily gastric lavage and intravenous glucose supplemented by vitamins were instituted. An x-ray study of the gastrointestinal tract revealed a marked deformity of the duodenal cap with practically complete pyloric obstruction probably due to scar formation. There was almost complete retention of the barium meal after six hours. The gallbladder was adequately visualized but of poor density due to the prolonged retention of the dye in the large dilated stomach. A surgical consultation advised intervention, which the patient promptly rejected. After three days of rectal feeding, intravenous glucose and vitamins, duodenal tube feedings were begun but unfortunately the patient soon removed the tube because of a sore throat and ear ache. She was then given and retained a milk-orange juice-gelatin mixture in small quantities every two or three hours plus Maalox® at regular intervals. The gastric analysis showed 67 units free and 85 units total acid with considerable residue. At this stage of her illness, the diet was increased to include well cooked cereal, egg albumin, custard, jello and she was started on Sippyplex® powder one teaspoonful in water at frequent intervals. She was discharged from the hospital improved and continued to improve at home in spite of another emotional disturbance while following the diet and medication. When last seen on 23 May 1957, ten months after discharge from the hospital, she was very comfortable. Her weight had increased to 104

lbs. and the hemoglobin was normal. A final gastric analysis showed 30 units free and 56 units total acid.

Here one noted good results with Sippyplex, aluminum gel and sedatives (syrup atarax).

Case 3:—H. R., male, 59 years of age, weight 162½ lbs., blood pressure 132/82, consulted us on 2 February 1956, because of heartburn, bloating and constipation. The former was also present during the night and was relieved by warm milk. He had been under severe emotional stress for the past 14 months and was smoking at least one pack of cigarettes daily. Physical examination revealed tenderness in the gallbladder region, Murphy and Boas signs positive, the liver was palpable two fingers' breadth below the right costal margin. Rectal examination showed a spastic anal sphincter and a moderately enlarged prostate. The hemoglobin was 83 per cent; red blood cells 4,210,000; white blood cells 13,900 with a normal differential. Other normal findings included platelet count, bleeding time, coagulation time, sedimentation rate and fasting blood sugar. The cholesterol was 330 mg. and the amylase 98 Somogyi units/ml. The stool was positive for occult blood after a three-day meat free diet and contained occasional fatty needles and undigested food. Sigmoidoscopy revealed some hyperemia of the mucosa and small internal hemorrhoids. A Papanicolaou smear of the stool showed epithelial cells of the inflammatory type, histiocytes and occasional polymorphonuclear leucocytes. There were no neoplastic type cells.

The patient refused a gastric analysis. Fluoroscopy and roentgenoscopy demonstrated a duodenal ulcer and an hiatus hernia. The gallbladder study and barium enema were negative except for multiple diverticula in the descending colon. The patient was placed on Sippyplex® one to two teaspoonfuls in milk or water several times daily in addition to a low residue diet and Trevidal® tablets. Within three days his symptoms had abated and when seen several weeks later he had improved. He was advised to continue the above regimen.

Case 4:—J. S., male, 34 years of age, weight 143 lbs., blood pressure 108/72 was first seen 21 January 1957, complaining of epigastric pain radiating to the mid back, heartburn, belching and bloating of four weeks' duration. He had been liberated from a concentration camp five years previously.

The physical examination was negative except for epigastric tenderness. A fasting gastric analysis showed 64 units free and 76 units total acidity and contained bile, mucus and occult blood. The stool on a meat free diet was likewise positive for occult blood.

X-ray examination demonstrated a duodenal ulcer with evidence of hypersecretion and marked gastritis.

The patient was placed on Sippyplex® and an anticholinergic with phenobarbital given several times daily to be repeated during the night if awakened. He was very nervous and apprehensive concerning the possibility of cancer.

After one month there was some improvement even though he still had a high gastric acidity. Another month later he was markedly improved but developed dysuria which was not relieved until both the anticholinergic medication and Sippyplex® were discontinued. The urine was alkaline and contained phosphate crystals. When last seen several months later he was completely symptom-free and cheerful without pain or heartburn.

Case 5:—V. S., male, age 25, weight 145 lbs., blood pressure 120/80 was first seen on 4 December 1956, because of a "nervous stomach" with such vague complaints as gas, belching and constant heartburn. For the past two years he complained of abdominal pain, vomiting and had lost 17 lbs. The pain appeared ½ hour after eating and lasted about one hour.

The physical examination, including a rectal examination, was negative except for epigastric tenderness and a positive succussion sign in the stomach, the greater curvature being well below the umbilicus.

A fasting gastric analysis showed 53 units free and 61 units total acid with traces of bile and a small amount of food residue. The stool was negative for occult blood and contained a few fatty needles with a moderate amount of mucus. The urine was negative; hemoglobin 89 per cent; red blood cells 4,490,000; white blood cells 12,000 with a normal differential. The bleeding time, coagulation time and fasting blood sugar were all within normal limits.

Films taken in February 1956, showed a duodenal ulcer. X-rays taken December 1956, showed a duodenal scar, gastritis and dilatation of the stomach with partial obstruction. Repeated gastric lavages plus anticholinergic medication and a bland diet relieved the patient to some degree but he soon developed a recurrence of pain, heartburn, nausea and vomiting. He was taught to perform stomach lavages at home and was placed on Sippyplex® and Bellafoline®. After two days, the Sippyplex® was discontinued because of urine alkalinity and dysuria.

Case 6:—H. G., male, 28 years of age, weight 120 lbs., blood pressure 110/70 presented himself on 3 December 1956, with a history of diarrhea while residing in Israel and severe heartburn relieved by bicarbonate of soda. He was very "nervous" because of his approaching marriage.

Physical examination showed epigastric tenderness, *diastasis recti* and a small umbilical hernia. The urine was negative and the hemoglobin 88 per cent. A fasting gastric analysis revealed 76 units free and 98 units total acid. Occult blood was three plus in the gastric contents and one plus in the stool.

X-ray examination showed marked spasm at the cardiac end of the esophagus with a small fleck of barium remaining in the duodenum which was tender under the fluoroscope. A 24-hour film showed marked spasm and several small diverticula in the colon. The patient was given a milk-orange juice mixture and

a combination of magnesium oxide two drams and bismuth subcarbonate four drams in eight ounces of water, a tablespoonful of which was to be taken ½ hour before meals.

On 10 December, he felt better and boiled chicken, stewed fruits and boiled fish were added to his diet. Although improved, he had lost 5 lbs., the hemoglobin dropping to 83 per cent and he again complained of epigastric pain. He was then placed on one teaspoonful of Sippyplex® four to five times daily. In spite of subjective improvement, he continued to lose weight which now reached a new low of 111 lbs., attributed to the approaching wedding date.

Reassurance in regard to cancer, sufficient rest, increasing diet and Sippyplex® brought about improvement in weight, appearance and a happier outlook on his future life. A gastric analysis a few days before his nuptial showed 5 units free and 17 units total acidity.

Case 7:—M. I., male, 29 years of age, weight 158½ lbs., blood pressure 128/72 appeared in February, 1957 with a history of nausea, epigastric pain associated with alternating diarrhea and constipation of five weeks' duration. He was given Gelusil®, antispasmodics and a bland diet with some relief for a short period of time.

Physical examination showed epigastric tenderness and abdominal distention. The liver was felt two fingers below the right costal margin. Rectal examination, urinalysis and hemoglobin were all negative. Fasting gastric analysis showed 42 units free and 65 units total acid. Occult blood was one plus in the gastric contents but negative in the stool. X-ray revealed a cloverleaf deformity of the duodenum, the 24-hour film showing some spasticity. The gallbladder series was negative.

He was placed on a modified ulcer diet with anticholinergic medication and Sippyplex® powder 2 teaspoonfuls several times daily for a period of one month.

When again x-rayed he showed less spasticity and less tenderness of the duodenum. His diet was increased and the Sippyplex® continued. He returned in four weeks completely symptom-free.

Case 8:—S. K., male, 53 years of age, presented himself on 25 September 1956, after being hospitalized for two weeks said to be due to a bleeding duodenal ulcer. A complete x-ray examination of the gastrointestinal tract including sigmoidoscopy and barium enema while in the hospital were all negative.

His past history was irrelevant except for an attack of malaria while in a concentration camp in 1944. The physical examination and laboratory findings including stools for occult blood were all negative.

The patient's complaints were typical of an ulcer consisting of postprandial pain and heartburn with nocturnal exacerbations which were relieved by warm milk. He was placed on a modified diet, anticholinergic and antacid medication gaining in weight although still experiencing epigastric pain.

X-ray study one month later revealed a definite duodenal ulcer crater. The gallbladder series was negative. He was then given Sippyplex® 1 teaspoonful several times daily preferably 2-3 hours after meals plus ¼ grain of phenobarbital.

During the following months his weight improved steadily, gaining a total of 17 lbs., with complete relief of the heartburn and epigastric pain. Sippyplex®, however, had to be reduced in frequency and taken intermittently because of alkalinity of the urine and dysuria.

Case 9:—H. M., male, 47 years of age, weight 150½ bls., blood pressure 130/75 was a highly emotional apprehensive individual who consulted us on 11 May 1954, because of "spasms" in the stomach, pain, heartburn and moderate constipation. He was awakened at night by the pain and an urge to void frequently. He presented himself with x-ray films with a diagnosis of a "penetrating" ulcer, pylorospasms and edema of the pyloric area.

The physical examination showed definite tenderness in the gallbladder region, Murphy sign positive, the liver was felt two fingers below the right costal margin. Rectal examination and urinalysis were negative, the hemoglobin 72 per cent.

He was admitted to the hospital on 18 May 1954. A gastric analysis showed marked hyperacidity and a positive reaction for occult blood in both the stomach content and the stool. X-ray examination showed a deformity of the duodenal cap produced in part by a prolapse of the gastric mucosa through the pylorus and in part by scar deformity. No ulcer crater could be demonstrated at this time. There were slight changes in the gastric mucosa consistent with a diagnosis of hypersecretion and gastritis. Gastric evacuation was completed before six hours and the progress of barium through the small and large intestines as observed up to 24 hours failed to reveal any definite pathological findings.

He was placed on a milk-orange juice-gelatin mixture and given 1/150 grain of atropine sulfate by injection at 8 A.M. and 9 P.M. intravenous glucose containing Berocca® and 2 teaspoonfuls of Maalox® by mouth every four hours.

The patient improved considerably and was discharged from the hospital in three weeks with a hemoglobin of 92 per cent. He continued to improve for the next six months when he had a recurrence of pain associated with severe heartburn and abdominal distention. He had lost weight; the hemoglobin dropping to 76 per cent. Sippyplex® was then prescribed with good results for the next ten months.

He was again hospitalized because of profuse gastric hemorrhage and melena. The hemoglobin was now 40 per cent, red blood cells two million. He received several transfusions, was placed on a Meulengracht diet supplemented by vitamins, and was given parenteral liver and iron, continuing with the Sippyplex® powders.

X-ray at the hospital showed a ½ to 1 cm. constant ulcer crater with irritability of the duodenum and swelling of the duodenal mucosa. Gastric evacuation was almost complete in one hour and the progress of barium through the small and large intestines as observed at frequent intervals up to 24 hours was not remarkable.

He made an uneventful recovery and continued to improve after discharge from the hospital, the hemoglobin reaching 81 per cent. Several months later he developed an acute exacerbation of active bleeding plus the original ulcer pain, heartburn and distention after having taken aspirin and Bufferin® for a "cold". The hemoglobin dropped to 68 per cent and he lost weight. Treatment with parenteral B_{12}, an oral iron preparation and Sippyplex® resulted in a prompt recovery. He was advised to give up the worry and hard work connected with his grocery store and seek other gainful employment. When last seen two months later he had fully recovered and had reached a normal weight and hemoglobin.

Case 10:—J. S., male, 63 years of age, weight 168 lbs., was first seen 20 February 1956, six weeks after a recurrence of bleeding from an old duodenal ulcer diagnosed five years ago. The first attack of active bleeding manifested by hematemesis and melena occurred two years ago at which time he was hospitalized and surgery advised.

Physical examination was negative except for an umbilical hernia, a blowing mitral systolic murmur and a hard firm prostate. The laboratory findings showed a hemoglobin of 83 per cent, red blood cells 3,960,000, white blood cells 11,300 with a normal differential. Other normal findings included the urine, fasting blood sugar, platelet count, coagulation, bleeding, and prothrombin time.

X-ray study showed an old duodenal ulcer with herniation of the gastric mucosa through the pylorus and findings consistent with a diagnosis of gastritis. He was placed on a Meulengracht diet supplemented by a milk-orange juice-gelatin mixture and given one tablet of Trevidal® every three hours. A well fitting abdominal support afforded relief for the ventral hernia.

Two months later following an emotional disturbance and indiscretions in diet, the stools became tarry and the hemoglobin dropped to 66 per cent. He was treated successfully at home by one of us (B. W.) during the active phase of the bleeding with 500 mcg. of B_{12} by injection and two C. V. P. and K. capsules p.c.,t.i.d. daily. He was soon placed on a definite ulcer regimen consisting of a modified ulcer diet and 2 teaspoonfuls of Sippyplex® three to four times daily.

Improvement was continuous and uneventful during the ten-month period of observation at which time he maintained a normal weight and hemoglobin level.

Summary

Ten selected cases from a study involving 110 patients have been reviewed in clinical detail. All of these patients were treated or are continuing treatment on Sippyplex® with good results.

Two patients had to discontinue Sippyplex® for a while due to alkalinization of the urine and irritation while voiding.

Gastric analysis after Sippyplex® showed variations in gastric acidity. After discontinuance of the powder there was no definite or stationary reduction of acidity.

Side-effects were minimal. There was an occasional case of constipation, occasional diarrhea and/or urinary irritation due to alkalinization of the urine.

GAS IN THE ABDOMEN: THE PART PLAYED BY THE NERVOUS SYSTEM*

JULIUS BAUER, M.D.†
Los Angeles, Calif.

Several decades ago aërophagia was a very popular clinical diagnosis. It was made in persons who complained of discomfort and bloated feeling in the upper abdomen, of belching and flatulence without any detectable organic disease but with manifestations of nervousness. It was made whether or not abnormal accumulation of gas in the stomach or colon could be seen with x-rays. A French clinician, Mathieu[1], reported on a patient who belched 5,000-6,000 times within several hours, and on another who passed thousands of flatus during 24 hours. It was strange, however, that the patients never had been seen to swallow air and did not have a bloated meteoristic abdomen.

I never believed that swallowing air can be of great importance in such conditons and felt that the term "aërophagia" is a misnomer[2]. It has actually been shown[3] that air is sucked into the esophagus during inspiration rather than swallowed with food if the superior esophageal sphincter is not closed as it normally should be. Some persons are able to consciously relax this sphincter and aspirate air particularly if they inspire against a closed glottis. Laryngectomized patients can learn to use this esophageal air for speech. Ventriloquists make use of the same mechanism which also serves a legitimate purpose though only for entertainment. In neurotic air-suckers, however, it is a source of suffering and complaints and psychoneurotics might avail themselves of it as a symbolic expression of their inner conflicts. It is noteworthy that such habitual belchers usually do not have a large fundus of their stomach distended by gas because they expel the aspirated gas before it reaches the stomach.

Where then does the gastric and intestinal gas come from, that piles up in excessive amounts, particularly in the left flexure of the colon, in some nervous, tense individuals? These people usually are not habitual belchers. Fermentation certainly plays but a minor role and is operative in organically healthy persons only under well known dietetic conditions. Some surgeons believe that swallowed or aspirated air also is responsible for the accumulation of gas in the colon. Maddock et al[3] have demonstrated that air aspirated into the stomach of experimental subjects reached the cecum in an average of 14.6 minutes and was passed as flatus in 30 minutes. It passes therefore rather rapidly through the gastrointestinal tract; not rapidly enough, however, to explain the accumulation

*Read before the Southern California Regional Meeting of The American College of Physicians, Santa Barbara, Calif., 24 February 1957.

†Clinical Professor of Medicine, College of Medical Evangelists, Los Angeles, Calif.

of gas in the previously empty intestines within a few seconds during pyelography.

It does not explain either the composition of intragastric or intraintestinal gas which differs substantially from the composition of air. Gas collected from the stomach or anus always contains much more CO_2 than air. This has been found by Schierbeck[4] as far back as in 1892 and has been confirmed since by many investigators. Whereas the sucked-in air may contain 0.04 to 0.1 per cent CO_2, 20-21 per cent O_2, and 79 per cent N, gas aspirated from the stomach of a patient undergoing intravenous pyelography contained 1.7 per cent CO_2 (Maddock). In cases of acute dilatation of the stomach (Woodyatt and Graham[4], 1912) gastric gas consisted of 24 per cent CO_2, 4 per cent O_2 and 72 per cent N. Analyses of flatus revealed in normal persons CO_2 10.3 per cent, O_2 0.7 per cent and N 59.4 per cent (Fries[4]). The rest are H_2, CH_4 and other gases derived from decomposition of food. After injection of room air into the human colon, the CO_2 content of collected flatus rises progressively with simulated altitude. At the altitude of 25,000 feet the flatus may contain 40 per cent CO_2; at 35,000 feet up to 80 per cent CO_2 within 10 minutes[5].

These established facts evidently prove that there is an exchange of gases absorbed in the circulating blood and those in the gastrointestinal lumen. This exchange takes place according to the partial pressure of the gases, their gradient and their diffusions coëfficient (R. Schoen[4]). The diffusion rate of CO_2 is 30 times greater than that of O_2, N being the least diffusible gas. That even N may diffuse from the intestinal lumen into the blood has been shown in experiments with inhalation of pure O_2. The partial pressure of N in arterial blood amounts to about 570 mm. of Hg. and is about equal to that of air and of intestinal gas. If only O_2 and no N is inhaled the partial pressure of N in the blood may fall rapidly and drop as low as to about 31 mm. Hg. within 4 hours. Consequently the gradient of N-pressure between intestines and blood increases; N diffuses from the intestines into the blood. This process has been used for the treatment of meteorism by reducing the gas volume in the intestinal lumen.

Any alteration of the gradient of the respective partial pressures of gases in the blood and intestinal lumen must lead to respective exchange and herewith reestablishment of balance. A. Oppenheimer[6] studied roentgenographically the rapid filling with gas of the stomach and intestines following ureteral catheterization and distention of the renal pelvis with fluid or oxygen. He recognized that the primary effect of these urological procedures must be atony of the hollow viscera brought about by inhibitory reflexes which arise from the urinary tract and may likewise originate from any painful abdominal structure. He explained the filling with gas as the result of rapid expansion of the small amounts of gas always present in the hollow viscera. He did not draw the obvious conclusion, however, that this event, that is, the expansion of intraluminal gases must decrease their partial pressure and consequently increase the gradient of gas

pressures from the blood to the visceral lumen. Gas with the highest diffusion coefficient, and that is CO_2, will diffuse first and in greatest quantity into the visceral lumen, N, the much less diffusible gas, will lag behind. This interpretation is consistent with all the facts so far known. The urologist Begg[7] offered a similar theory but considered N as the chief gas migrating in and out between the intestinal lumen and the circulating blood according to the variable tonus of the viscus and hence its variable pressure gradient. In fact, it is CO_2 rather than N that reestablishes the pressure balance most efficiently.

It stands to reason, that any relaxation of the tonus of a part of the gastrointestinal tract, whether it did or did not contain some gas before, must necessarily lead to diffusion of gas from the blood. Relaxation, that is hypotonicity of the viscus not immediately filled with food or fluid results in a diminution of intraluminal pressure. Gas is sucked in from the circulating blood the quantity of which depends on the degree of relaxation.

The fundamental point of this concept and its principal difference from the still popular concept of "aërophagia" is this: Diminution of the muscle tonus of the hollow viscus comes first, accumulation of gas occurs as its consequence; for adherents of aërophagia this would occur in the opposite order.

The muscle tonus of the gastrointestinal tract varies almost continuously, not only under the impact of food but under the influence of its autonomic innervation. Spastic contraction of any part of the viscus is automatically associated with relaxation of the tonus of the adjacent parts. What is known as "irritable colon" or "irritable duodenum" without organic disease has been recognized as a manifestation of autonomic nervous imbalance, as response to excessive stimulatory or inhibitory nervous impulses. The lumen of the viscus is in some parts quite narrow, the viscus is in a hypertonic, spastic state, in other parts its caliber is increased, its tonus diminished. Atonic dilatation and spastic contraction go hand in hand.

Reflex relaxation of the tonus originating from various acutely painfully diseased organs has previously been mentioned. Nervous, irritable persons are particularly prone to gas accumulation during pyelography. Maddock[3] aspirated about three times as much gas from the stomach of nervous as from that of calm subjects during pyelography.

Without entering into the discussion as to how far the parasympathetic, the sympathetic and the intrinsic nervous plexus within the intestinal wall are involved in the determination of the varying tonus of the hollow viscera, one special type of gas accumulation in the gastrointestinal tract should be mentioned that has been described by the Hungarian clinician R. Bálint[8] (1917) as *tympanismus vagotonicus*. It is accompanied by bradycardia and respiratory sinus arrhythmia. Atropine abolished both the bloating and the bradycardia.

One of my patients, a 20-year old college student, presents such *tympanismus vagotonicus* in classical form. He is a tall, (6′ 3″) slender, highly intelligent but nervous honor student who was found to have bradycardia and sinus arrhythmia at the age of 9, and a very large, gas filled gastric fundus first at the age of 11 years. With this sometimes enormous gas accumulation in the fundus is associated varying pylorospasm and spastic, irritable duodenum. There is no evidence of an organic lesion and there are usually no symptoms. Swallowing air could not be observed during fluoroscopy. Pulse rate varies a great deal. It is usually 52-60 but was found once to be only 44, another time 92 standing. Considerable slowing down of the pulse rate occurred on stooping (Erben's sign). Blood pressure varies between 108 and 125 systolic, and 60 to 45 diastolic. ECG shows nothing abnormal except sinus bradycardia. The boy has always been an enthusiastic sportsman. A few times he suffered from an "upset stomach", once, on a trip through Utah, from colicky pain in the right upper abdominal quadrant. Kidney stones were suspected there but not found, and all the tests were negative. Another episode of abdominal cramps was associated with diarrhea and subsided spontaneously as the first one within a few days. He is not a belcher.

This case of *tympanismus vagotonicus* demonstrates particularly well that the underlying autonomic nervous imbalance may exist as a constitutional trait without accompanying or even causative emotional factors. If there are symptoms it may be designated as vegetative neurosis as contrasted with psychoneurosis.

It is not within the scope of our discussion to elaborate on psychoanalytical aspects of meteorism, neither on the participation of a variable tonus of the striated abdominal muscles and the diaphragm in the symbolic conversion of emotional conflicts into this type of somatic expression. It may suffice to have emphasized the importance of gas diffusion between blood and gastrointestinal lumen as the main though not the only factor of gas accumulation within this lumen and the role of the nervous system played in this mechanism.

Summary

1. What is usually designated as aërophagia has been proved by previous authors to be accumulation of gas in the stomach not swallowed but sucked-in during inspiration.

2. Although this gas may rapidly pass through the intestinal tract it cannot explain the occasionally almost instantaneous appearance of gas in the colon under certain circumstances, e.g. pyelography.

3. Neither can it explain the very different composition of gastric and intestinal gas as compared with that of sucked-in air.

4. This is understandable only by diffusion of blood gases into the lumen of the hollow viscera if relaxation of their wall has led to a negative pressure and consequently to diffusion from the circulating blood according to the pressure gradient and the diffusion coefficient of gases. CO_2 has the greatest diffusion coefficient and for this reason is found consistently in much higher concentration in gas containing abdominal viscera than in air.

5. Relaxation of the visceral muscle tonus and spastic contractions of a viscus go hand in hand and depend on regulation by the autonomic nervous system. Hence the frequent gas accumulation in persons with autonomic nervous imbalance which may or may not be the result of emotional imbalance, that is, psychogenic in nature.

6. One type of a nonpsychogenic excessive gastric gas accumulation is represented by Bálint's *tympanismus vagotonicus* associated with bradycardia.

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POLYCYSTIC DISEASE OF THE LIVER*

MAURICE FELDMAN, M.D.

Baltimore, Md.

Polycystic disease of the liver is a comparatively rare condition. In 1,319 adult autopsies we found 7 cases, an incidence of 0.53 per cent. In a recent communication, Morgan and Feldman studied 74 autopsied cases in the aged, between 75 and 95 years, found two instances of polycystic disease of the liver. In 6,141 autopsies, Ackman and Rhea found 10 cases of polycystic disease of the liver, an incidence of 0.16 per cent. In 11,245 autopsies Brown found 36 cases of polycystic kidneys, 8 of which were associated with polycystic disease of the liver.

Polycystic disease of the liver is due to a congenital embryological maldevelopment of the bile ducts. It is frequently associated with polycystic changes in the kidneys, and occasionally coexists with cystic changes in other organs. It more commonly involves two or more organs. Besides the kidneys and liver, next in order of frequency are the pancreas, spleen, lungs and ovaries. In an analysis of 374 collected cases of polycystic disease of the liver, there were 193 cases associated with polycystic kidneys, an incidence of 51.6 per cent. Of 169 collected cases of polycystic kidneys, 50 were associated with polycystic disease of the liver, an incidence of 34.3 per cent. Moolton found 19 per cent, and Oosting 30 per cent of polycystic kidneys were associated with polycystic disease of the liver. These data indicate that polycystic disease of the liver is more apt to be associated with cystic disease in other organs than polycystic kidneys.

Polycystic disease of the liver is infrequently involved alone. In our 7 cases, it was involved alone in only 1 instance. In Comfort's et al 24 cases, the liver was involved alone in 8 instances. In our 7 cases of polycystic disease of the liver, besides the 1 case in which the liver was involved alone, it occurred in the liver and kidneys in 1 case, the liver, kidneys and pancreas in 1 case, the liver, kidneys and ovary in 1 case, and the liver and pancreas in 3 cases. Of the above 7 cases, the polycystic disease of the liver was associated with polycystic kidneys in 3, and cysts of the pancreas in 4 cases. Rall and Odel reported 4 instances, Bunting, and Sears, each 1 case, which coexisted with cysts of the pancreas. Rall and Odel, and Henson et al reported an instance of cystic disease of the spleen, and Brown 1 case of cyst of the lung associated with polycystic disease of the liver and kidneys. In 1 of our 7 cases the ovary was involved. In Morrin's case of polycystic liver, there was an associated parovarian cyst in the broad ligament.

*The author is indebted to Dr. Tobias Weinberg, head of the Department of Laboratories of the Sinai Hospital, for the privilege of reviewing the necropsy records.

Polycystic disease of the liver is characterized by multiple cysts of varying sizes scattered throughout the liver. In some instances the cysts are so numerous and widespread that they appear to have destroyed the parenchyma of the liver. The cysts vary in size from a pinhead to that of a lemon or larger. At times individual cysts may measure as large as 6 cm. in diameter. They are thin-walled, epithelial lined, filled with a clear watery fluid. The cysts may be confluent and multilocular. Both lobes of the liver are frequently involved, but it more commonly occurs in the right lobe and less often in the left lobe. Clagett and Hawkins reported a case in which the whole left lobe of the liver was involved. The size of the liver varies from normal to one that may fill the entire abdomen. The liver is considered to be enlarged if it weighed over 2,000 gm. Of 31 cases of polycystic livers, Bell found 15 cases with an enlarged liver, the largest weighing 9,510 gm. Latimer reported an instance in which the liver weighed 8,806 gm. (19.5 pounds). Clark and Westfall a case with a liver weighing 4,360 gm.

Occasionally polycystic disease of the liver is associated with other developmental anomalies and complications. Moolton reported a case associated with atresia of the bile ducts; Waterson and Morgan a case with jaundice, Deutsch a case complicated with cholangitis, and Crismer and Lambermont a case associated with portal stasis. Willis reported a case of polycystic disease of the liver complicated by a carcinoma arising in the epithelial lining of the cysts.

Polycystic disease of the liver is observed in all ages, from infancy to old age. Most cases are recognized between the fourth and fifth decades. The condition has been found in the newborn and stillborn infant. Sears, Urich and others have reported single cases occurring in the stillborn, and Moolton an instance in a newborn infant. The condition more commonly occurs in females. In Henson's et al 29 cases, 23 were females and 6 were males. The hereditary tendency of the development of polycystic disease is well known. Numerous instances have been recorded of the condition occurring in the same family. Bunting reported 2 cases of the same mother.

Polycystic disease of the liver is more commonly recognized at autopsy. It has been diagnosed at surgery, and also by peritoneoscopy and biopsy examinations of the liver. Clinically the condition pursues a slow progressive course, with gradual enlargement of the liver. One of the characteristics of the condition is the general good health of the patient accompanied by an enlarged liver. The condition rarely causes functional impairment of the liver. In some instances, however, where there is marked parenchymal liver cell destruction there may be measurable functional impairment. Niemetz et al reported 2 instances which yielded evidence of impaired liver function. In Comfort's et al 24 cases of polycystic disease of the liver, 13 presented symptoms referable to the liver. In Henson's et al 29 cases, physical examination revealed a mass in 23 cases (79 per cent).

There are no characteristic roentgen signs indicative of polycystic disease of the liver. When the liver is markedly enlarged, its size can be depicted. It may produce pressure signs upon adjacent viscera suggesting liver pathology. Displacement of the duodenum, stomach and hepatic portion of the colon has been observed. The right diaphragm may be elevated in some instances.

Conclusions

1. The adult autopsy incidence of polycystic disease of the liver was found to be 0.53 per cent.

2. About one-half of the cases of polycystic disease of the liver are associated with polycystic kidneys.

3. About one-third of the cases of polycystic kidneys are associated with polycystic disease of the liver.

4. Polycystic disease of the liver is rarely involved alone, is more apt to be associated with cystic changes in other organs.

5. Enlargement of the liver occurs in about one-half of the cases.

6. Most cases of polycystic disease of the liver are recognized at autopsy. It can be demonstrated at surgery and by peritoneoscopy and biopsy examinations. Clinically the condition can be suspected by the presence of an asymptomatic enlargement of the liver.

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EFFECT OF ANTI-INFLAMMATORY HORMONES UPON THE PANCREATITIS PRODUCED BY STYLOMYCIN AMINONUCLEOSIDE

HANS SELYE, M.D.*

Montreal, Canada

It is well known that, occasionally, pancreatitis—accompanied by liponecrosis of the surrounding tissue—may occur in patients treated with large doses of anti-inflammatory hormones such as cortisone and its derivatives, or after exposure to acute stress (for literature, see Selye[1]; Selye, Horava and Heuser[2]). More recently, using the newly synthesized cortisol derivative, 2-methyl-9(α)-chloro-cortisol, we have been able to produce selective necrosis in the pancreatic fat tissue of the rhesus monkey, although this was not accompanied by any pronounced inflammatory changes[3].

It is the object of this communication to report upon experiments which revealed that subcutaneous injections of stylomycin aminonucleoside, "SAN" (6-dimethylamino purine, 3-amino-d-ribose), can produce a purulent pancreatitis in the rat, and that simultaneous treatment with anti-inflammatory hormones fails to prevent this type of inflammation. Indeed, ACTH and cortisol actually tend to aggravate this pancreatitis, presumably because they enhance the occurrence of pancreatic fat necrosis.

The literature concerning stylomycin and its aminonucleoside is somewhat confusing because of the fact that this antibiotic was first called "achromycin" (a name which now designates another antibiotic)[4] and then, "puromycin"[5-7] before it was given its current name "stylomycin". Little is known as yet about the pharmacology of stylomycin apart from its efficacy in the treatment of infections, particularly those caused by certain trypanosomes. It has been noted, however, that both stylomycin and its aminonucleoside can produce a nephrosis-like syndrome with renal lesions, subcutaneous edema, pleural fluid, ascites, hyperproteinemia, hyperlipemia, and azotemia in laboratory rodents[4,6]. This condition is apparently accompanied by increased aldosterone secretion[7].

Studies concerning the pathogenesis and treatment of acute purulent pancreatitis have been handicapped by the difficulty of reproducing this disease in experimental animals, by means other than the topical application of mechanical or chemical irritants to pancreatic tissue. Therefore, a technic that permits the consistent induction of purulent pancreatitis by subcutaneous treatment with a drug appeared to be worth recording.

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*From the Institut de Médecine et de Chirurgie expérimentales, Université de Montréal, Montreal, Canada.

Materials and Technics

Sixty female Sprague-Dawley rats, with an average initial body weight of 100 gm. (range 92-110 gm.), were subdivided into 3 equal groups, all of which received Stylomycin aminonucleoside (SAN) at the daily dose of 2 mg. in 0.2 ml. of water, subcutaneously. *Group I* was not otherwise treated; *Group II* received (in addition to the SAN) cortisol acetate, or COL-Ac ("Cortril", *Pfizer*), in the form of hydrocortisone acetate microcrystals, at the daily dose level of

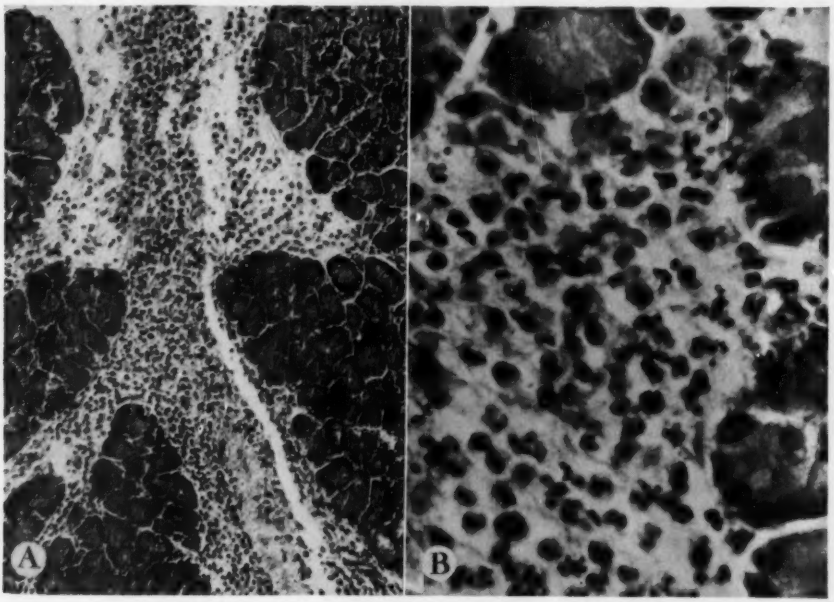

Fig. 1a Fig. 1b

Fig. 1—A. Purulent interstitial pancreatitis in an animal of Group I (x 120).—B. Higher magnification of an area from the pancreas shown in A. Note numerous polymorphonuclear leucocytes between the pancreatic acini (x 580).

1 mg. in 0.2 ml. of aqueous vehicle; *Group III* received (in addition to SAN) ACTH ("Duracton", Nordic Biochemicals) at the dose of 10 I.U. in 0.5 ml. of water, subcutaneously, twice daily. The animals were fed on "Purina Chow" and the experiment was terminated, after 14 days of treatment, by killing the rats with chloroform. Immediately after autopsy, the kidney and pancreas were fixed in Susa solution for the subsequent histologic study of paraffin-embedded sections stained with hematoxylin-eosin.

Results

After the 10th day of treatment, it became evident that the SAN had produced the expected water retention, in all three groups. Although the controls were somewhat less severely affected than the rats given COL-Ac or ACTH, there was marked swelling of the abdomen due to ascites, and pitting subcutaneous edema.

Autopsy confirmed these observations and showed, in addition, that a large amount of pleural fluid had accumulated in most of the SAN-treated rats and, particularly, in those which had received COL-Ac or ACTH in addition to SAN. Furthermore, in the latter 2 groups, there were white chalky patches around the pancreas and, to a lesser extent, throughout the mesenteric and retroperitoneal fat tissue.

Histologic examination revealed purulent interstitial pancreatitis in the animals of all 3 groups, but the lesions appeared to be even more diffuse in the rats given anti-inflammatory hormones (Groups II and III) than in the controls (Group I). Furthermore, in the latter 2 groups, there was evidence of intense pancreatic fat necrosis (in the regions that, upon macroscopic inspection, appeared as chalky white spots), while in the controls treated with SAN alone, there was virtually no evidence of this change.

On first consideration, it may be surprising that two potent anti-inflammatory hormones should actually aggravate an inflammatory reaction such as a pancreatitis. It must be kept in mind, however, that under certain conditions, such a reversal of the effect of anti-inflammatory hormones has been observed before. For example, if an inflammation is produced with croton oil, in a region where the blood circulation is impeded by partial blood-vessel ligature, subsequent treatment with cortisol can actually increase the dimensions of the inflamed area[8,9]. It will be recalled that the same situation obtains in tuberculosis and other infections in which anti-inflammatory corticoids may augment the inflamed area, merely by enhancing the spread of the pathogenic organisms. It is quite possible that, in the present experimental series, the antiphlogistic hormones facilitated the spread of the toxic pancreatic juice that is liberated from damaged acinar tissue, and thereby enhanced the spread of inflammation and the production of liponecrosis.

In any event, it is clear from these observations that systemic treatment with SAN can consistently produce a purulent pancreatitis in the rat and that the accompanying liponecrosis is aggravated by antiphlogistic hormones.

Summary

Experiments in the rat showed that subcutaneous treatment with large doses of stylomycin aminonucleoside (SAN) consistently produces a purulent pancreatitis within about 14 days.

This inflammatory reaction of the pancreas was not inhibited by such antiphlogistic hormones as cortisol acetate (COL-Ac) or adrenocorticotrophic hormone (ACTH), under the conditions prevailing in these experiments. Indeed, it was somewhat aggravated, presumably because these hormones facilitate the spread of toxic pancreatic secretion and enhance the development of fat necrosis.

ACKNOWLEDGEMENTS

These investigations were carried out with the aid of grants-in-aid from the Pfizer Laboratories and the Lederle Laboratories who also supplied the stylomycin aminonucleoside. The author is also indebted to the Pfizer Laboratories for the cortisol acetate ("Cortril") and to Nordic Biochemicals for the ACTH ("Duracton") used in this work.

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IS MONILIA RESPONSIBLE FOR PRURITUS ANI, AND IF SO, TO WHAT EXTENT?

F. VOGEL, M.D.

Brooklyn, N. Y.

A review of the recent literature on pruritus ani is a discouraging and frustrating experience. Not that there are not enough papers written—there are plenty. Not that the quality of a good many of them is not of high standard and of exhaustive composition—among the many articles there are quite a number well-written and elaborate. What is so distressing is the lack of new thought in more recent articles. One could take the headlines, title and author, and almost exchange them at liberty. Going over those papers one finds more or less the same content and even the same phrases. They often begin with precisely the same words, such as: "Pruritus ani is not a disease, but a symptom-complex", or the like. No writer, however, has yet pointed out how he came to that conclusion and what research has formed his opinion. For nobody knows as yet what we are confronted with except for the invariably repetitious statement that it is "a bothersome condition which requires an abundance of patience from the patient and the patient's doctor". If you have read one elaborate paper you have read them all, with a few remarkable exceptions. It seems that proctologists at large accept without hesitation the general prevailing opinion as set forth by previous writers. Few authors writing on pruritus ani have undertaken to do a little research of their own in order to clarify the situation and shed light upon this condition. Amazingly few relate to dermatology which is the natural partner; dermatology is taboo. The dermatologist does not look into the rectum, or is not supposed to, therefore, his opinion is unwillingly heard. On the other hand, some dermatologic text books offer nothing but excerpts from what proctologists have had to say about pruritus ani.

The dogma of symptom-complex and complex treatment in these respective papers is usually followed by enumeration of etiologies which may be more or less complete and in similar or different order. This results in the establishment of an accepted classification handed down through the years, for which, however, there is no evidence. As a rule the classification divides pruritus ani into primary and secondary, or into idiopathic or those cases in which a cause seems to be apparent. The contradiction of naming a disease idiopathic and at the same time stating that it is no disease but a symptom-complex has not been disturbing so far. As if "idiopathic" would not—in many instances—be a confession of ignorance.

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*From Veterans Administration, Brooklyn Outpatient Clinic, Brooklyn, N. Y.; from the Department of Proctology of the New York Polyclinic Medical School and Hospital, New York, N. Y., and the Gastroenterological Clinic, Long Island College Hospital, Brooklyn, N. Y.

Fungus is named over and over again as one of the causes and, in addition, many times moniliasis; as if monilia were no fungus and as if the fungus correlated with pruritus ani were not monilia, i.e., sporidium albicans, etc., whatever name may be preferred. This attitude of credulity is the more incredible as there are several fine reports available on actual research.

How often does monilia really occur in pruritus ani and if so, is it the cause of the itch or only a secondary infection? This was one of the questions confronting us when we attempted to approach the puzzle of pruritus ani.

In a previous paper of this writer dealing partly with choleic changes in pruritus ani, some original work done by Sborov, Jay, Watson, and Schwartz was cited. These authors have by experiment and study, established that administration of certain antibiotics has a positive effect on the suppression or elimination of the normal colonic flora, which results in certain conditions in the colon and system similar to extrahepatic biliary obstruction; namely, the reduction or elimination of Vitamin B-complex and Vitamin K. This author has ventured the opinion that loss of Vitamin B resulted in colonic malfunction such as diarrhea and spasticity which has been observed to occur, while elimination of Vitamin K brings about reduced clotting formation and, therefore, tendency to bleed, also a not infrequent observation in these cases. Here the mechanism is different, but the effect is equal to biliary obstructions where absorption of the present Vitamin K is difficult or abolished. Also it was found that subjugation of the colonic flora removes the normal obstacle to overgrowth of monilia.

How often, then in comparison, is monilia found in pruritus ani other than after antibiotics? The answer derived from our observation was astounding. All the cases included in the study were full-fledged cases of pruritus ani with thickening of the perianal skin, molding and elevation of the radial skin folds, with grayish discoloration mostly on an underlying erythema. Also found were minute ulceroid surface defects, maceration of the perianal skin, and sloughing, extending over an area of about 2 to 6 inches in diameter. Most lesions were moist and shiny, some of them dry, but all afforded the picture of a chronic pruritus ani known to any examiner. The itch had been present for periods up to 16 years. Many, if not most of them, had been subjected to all sorts of treatment.

Despite anorectal pathology in a certain percentage of cases, this writer was unable to determine any etiological dependency as some cases continued after correction, nor could he classify the cases as tractables and intractables, or as primary or secondary, or idiopathic.

Among the 91 cases reviewed thus far within a period of over two years, only 9 cases, or less than 10 per cent, of monilia were established by perianal scrapings and culture. This contradicted grossly the recent generally accepted belief that practically all cases of pruritus ani are inflicted with this fungus. This

has been established before: M. R. Hill saw six per cent of fungus; only three per cent or less were conceded to by R. J. Jackman, who felt that fungus infection in pruritus ani had been overemphasized; E. T. Whitney in his fine contribution was "able to obtain but few questionable cultures of yeast or fungi taken from scrapings of the skin around the anus", and also mentioned that ". . . most authorities have considered it (pruritus ani) an epidermophytosis principally because the symptoms and the appearance of both have much in common . . ." Our impression was similar. Symptoms were alike in all cases with and without fungus. In other words, there was no difference in clinical appearance and behavior. Therefore, the question: How much does fungus contribute to itch, and is fungus a causative agent? From our findings it may be reasonably doubted.

A. C. Allen, a dermatologist, believes that the cutaneous lesions are allergic manifestations caused by absorption of the allergenic products released by the fungus in remote areas of the system and transported by the blood stream or otherwise. No topical fungus is found in these cases but may be present in a different part of the body. This is called the id phenomenon. This, however, is hypothetical and has not been reasserted within this study. Whitney was unable to confirm the id theory. Only a group of his cases showed remote fungus infection and if eradicated, pruritus ani lingered on nevertheless. Andresen believes that most cases of pruritus ani are on an allergic basis as a response to extrinsic allergenic substances.

It is not suggested herewith to follow this line without reservation. Allergy in itself is a physical dislike without explanation and there is still enough mysticism about its own etiology. Also in the series presented here other allergic manifestations play a minor role; at least the quest for allergies has been negatively answered by an overwhelming group of these cases, and eosinophilia was rare; eosinophilia, of course, is not a constant finding in allergy. Yet there is a strong case for allergic etiology. Whitney and his group who had the opportunity of histologic study of 20 odd, cases compared the findings with Sachs and Miller's classification of the histology in eczematous dermatoses and found them identical with atopic dermatitis, an allergic disease, and therefore, found the conclusion inescapable that pruritus ani is a dermatitis of allergic origin. The main findings were congestion (dilated capillaries) edema of the corium, and a thickening of both the epidermis and the corium. Also he found essential histologic differences from dermatophytosis. In addition, aggravation by large doses and amelioration by small graduated doses of histamine were accepted by them as confirmation of the allergic factor. This, however, will be a topic of a further discussion.

It is believed, however, that this study has shown that the general presumption of topical presence of monilia in pruritus ani is an error; that in a certain percentage of cases—less than 10 per cent in our series—secondary fungus growth may be expected. As to its contribution to the symptom of itch which

is equally present in all cases in the absence or presence of monilia, its importance may equally be questioned. At any rate, presumptions and statements taken from generation to generation should not be accepted in good faith indefinitely but should be thoroughly screened. Further examination should bring us a step closer to the solution of this intractable problem. It is hoped that this paper may stimulate further investigation.

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President's Message

Scope

In a discussion with a publisher a few weeks ago it was pointed out that one of the reasons for the success of his medical publications was that they covered broad fields such as medicine, surgery, nutrition, etc. In this respect gastroenterology appeared to him a rather restricted field—an opinion based on past concepts.

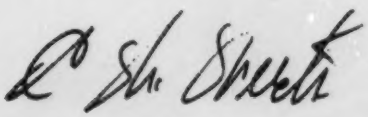
This concept seems untenable to us for several reasons. For instance, a survey has shown that the most frequent complaints bringing patients to the physician's office, or requiring admission to the hospital are referrable to the digestive system. Recently this has also been found to be the case in patients admitted to the hospital under the Blue Cross Plan. This certainly indicates a broad field rather than a limited one.

If there are limitations in the field of gastroenterology they exist in the area of definitive knowledge and not in the scope of unanswered problems. That the gastroenterologist is alert to this is indicated by how exercised he is regarding training and research in this field.

The training of the gastroenterologic internist makes the broadest demands of any branch of medicine. In addition to a thorough grounding in internal medicine this candidate is asked to be familiar with neuropsychiatry, endocrinology, biochemistry, nutrition, allergy and diagnostic radiology of the digestive tract.

The Subspeciality Board in Gastroenterology of the American Board of Internal Medicine has been established to formulate requirements for residency training facilities, to determine candidate eligibility for examination and to provide suitable subspecialty board examinations.

One of the most convincing facts indicating that gastroenterology is no longer a "limited" field is the development of its own study section in the National Institutes of Health in Bethesda. Because funds are now available through this channel for research grants, training grants and traineeship grants this section will very likely play an important role in shaping the future of gastroenterology.



Part of the group which participated in the Annual Convocation of the American College of Gastroenterology at The Somerset in Boston, Mass., 20 October 1957. Among those seated in the first row are: Dr. Arthur A. Kirchner, out-going president; Dr. C. Wilmer Wirts, president-elect; Drs. Frank J. Borrelli, Joseph Shaiken, Henry Baker and Louis Ochs, Jr., vice-presidents; Dr. James T. Nix, Chairman of the Board of Trustees; Dr. Henry G. Rudner, Sr., Chairman of the Board of Governors and Dr. Chester S. Keefer who received an honorary fellowship.

NEWS NOTES

Fellowship Keys

Keys for *Fellows* of the American College of Gastroenterology have been authorized by the Board of Trustees. An illustration of the key is at the left.

These may be ordered from the headquarters office, 33 West 60th Street, New York 23, N. Y., at $10.00 each including federal tax and shipping charges.

The reverse side of the key will be engraved with your name and the date of your election to Fellowship. Send your order today.

In Memoriam

We record with profound sorrow the passing of Dr. Adolph Baer of Pearl River, N. Y., and Dr. Maxwell H. Thurm of Brooklyn, N. Y., Members of the American College of Gastroenterology. We extend our deepest sympathies to the bereaved families.

ABSTRACTS FOR GASTROENTEROLOGISTS

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GASTROINTESTINAL TRACT

GASTROENTEROLOGY: Sara M. Jordan, Everett D. Kiefer, S. Allen Wilkinson, Francis E. McDonough, John R. Ross and John M. McGrath. New England J. Med. 255:1042 (29 Nov.), 1956.

This paper, in two parts, concerns itself with a panoramic survey of recent progress in the field of gastroenterology.

In the diagnosis of peptic ulcer the history and clinical picture are still of paramount importance despite the improvement in radiologic technics and gastroscopy. Ideal treatment is still medical, surgery being reserved for intractability of symptoms when caused by penetration, obstruction, perforation, uncontrollable hemorrhage, uncooperative patients and a reasonable suspicion of malignancy. Recent reports emphasize that the location of a gastric ulcer should no longer be considered significant in the differential diagnosis of malignant from benign lesions in the stomach. Subtotal gastrectomy is apparently still the operation of choice for peptic ulcer. Mention is also made of recent work correlating the effect of salicylates and the production of peptic ulcerations. There has been a re-emphasis of the relation of gastric cancer to pernicious anemia and a suggestion that while mass screening of the population for gastric cancer is not practical such tests would seem to be of value in those groups of patients who are achlorhydric or hypochlorhydric.

Several papers are reviewed that concern themselves with the nutritional role of the small intestine, particularly concerning the mechanism and role of specific areas of the small bowel in absorption. A number of reports would tend to indicate that tropical and nontropical sprue, idiopathic steatorrhea and celiac disease are varieties of the same disorder. Although considered a rare entity there have been an increasing number of papers on carcinoid and it is felt that with the use of the test for urinary 5-hydroxyindoleacetic acid more frequent diagnoses of carcinoid may be made.

L. A. ROSENBLUM

A STUDY OF 356 CARCINOIDS OF THE GASTROINTESTINAL TRACT: Richard A. MacDonald. Am. J. Med. 21:867 (Dec.), 1956.

The autopsy study of 356 cases of carcinoids collected from the files of seven Boston hospitals revealed 4 new cases of the carcinoid syndrome with attacks of

flushing of skin, telangiectasis of face, diarrhea, asthmatic bronchitis and gradual development of right heart valvular disease and right heart failure. All cases showed arthritic changes of the fingers and occasionally of other joints resembling rheumatoid arthritis. Mental disturbances in the form of uncooperative, unreliable, contradictory behavior was also noticed. The microscopic findings of the stenotic pulmonary valve differed from those seen in congenital or rheumatic disorders. There was a great increase of the fibrous tissue especially of the intercellular ground substance with normal endothelium and elastic fibers. No appendiceal carcinoid was observed that had spread beyond the local lymph nodes. Therefore, none was responsible for the carcinoid syndrome. No proven case of carcinoid syndrome following appendiceal carcinoid could be found in the English literature. Metastatic involvement of the liver with or without this syndrome in the presence of appendiceal carcinoid requires an additional extraappendiceal primary site of the carcinoid.

H. B. Eisenstadt

GASTROENTEROLOGY (CONCLUDED): Sara M. Jordan, Everett D. Kiefer, S. Allen Wilkinson, Francis E. McDonough, John R. Ross and John M. McGrath. New England J. Med. 255:1084 (6 Dec.), 1956.

This concludes the paper on progress in gastroenterology.

Progress in colonic disease has been confined to further elaboration and improvements in the x-ray examination of the lower bowel. It is to be observed that proctosigmoidoscopy has been adopted as a routine part of any complete medical survey.

Progress concerning ulcerative colitis apparently has been confined, in the main, to reports on the use and disadvantages of the steroid hormones. An increase in the surgical management of this baffling condition is also to be found. Several papers on a relatively rare postoperative complication, pseudomembranous enterocolitis, and its relation to antibiotic therapy are mentioned. The use of ACTH in this condition is discussed in several papers. The authors note that the trend in chronic and recurrent diverticulitis of the colon has been toward more frequent employment of surgical resection. That diverticula without cancer can cause gross bleeding was described in one well documented paper.

A number of papers dealing with the physiology and disease of the pancreas were reviewed and some of the newer tests used in diagnosis were mentioned. Several papers outlined in detail the medical therapy of acute and recurrent pancreatitis. There were a number of papers that were devoted to roentgenographic aids and methods of making an early diagnosis of cancer of the pancreas.

Recent work and publications on liver disease have been a recapitulation of previously published work or an attempt to clarify it. Noteworthy have been the reports on the use of L-glutamic acid in hepatic coma, especially where the blood ammonia levels are high.

L. A. Rosenblum

HIATAL HERNIA TREATED BY TRANSECTION OF THE PHRENIC NERVE: William Bates and John W. Egoville. Rhode Island M. J. 39:678 (Dec.), 1956.

The authors report a series of 49 cases of hiatal hernia treated and cured by primary phrenicectomy. Only one case required a repair because of the unsuccessful result obtained by phrenicectomy. The ages ranged from 32 to 74 years. The ratio of females to males was 8 to 1. Symptoms in many instances were present as long as 30 years.

The authors' series of cases showed a 93 per cent improvement of symptoms. Seven per cent showed no improvement and all showed disappearance of the hernia on x-ray study.

It is important in performing the operation not to leave behind an accessory phrenic nerve which comes off C 3 and occurs in 20 per cent of cases. About 3"-5" of the nerve and all its branches are removed, care being taken not to injure the thoracic duct.

The operation brings about the beneficial results by 1. decreasing the intragastric pressure, by increasing the intraabdominal

space 2. by elevating the diaphragm the stomach is reduced by the pull of the fixed left gastric artery 3. by permitting the greater curvature of the stomach to expand the gastroesophageal angle is restored allowing the sphincter mechanism to function with a cessation of the symptoms caused by regurgitation.

ALEXANDER ZABIN

ESOPHAGUS

CONGENITAL ESOPHAGEAL STENOSIS: Lester L. Vargas, Richard C. Britton and Edmund N. Goodman. New England J. Med., 255:1224 (27 Dec.), 1956.

A case of esophageal stenosis at the level of the cardia associated with a congenitally short esophagus in a seven-week-old infant is presented. The obstructing lesion consisted of an annular band of hypertrophic muscle. Treatment by extramucosal myotomy combined with intraluminal dilatation is described. The possible origin of the circular muscle bundle is discussed.

JACOB A. RIESE

PERFORATION OF PEPTIC ULCER OF THE ESOPHAGUS INTO THE PERICARDIAL CAVITY: D. D. Gellman. Brit. M. J., 5006:1413 (15 Dec.), 1956.

Chronic peptic ulceration of the esophagus is a well recognized complication of those types of hiatus herniae which allow regurgitation of acid gastric content into the esophagus. Like peptic ulcers elsewhere, if untreated, they may perforate. Usually such perforation occurs on the posterolateral aspect of the esophagus and may involve the mediastinum or the plural cavity. Rarely the pulmonary veins or aorta may become involved.

The authors describe a case of ulceration occurring on the anterior wall of the esophagus which perforated into the pericardial cavity. There are very few reported cases of esophageal lesions communicating with the pericardial cavity. All reported cases terminated fatally. The differential diagnosis in the cases reported lies between 1. myocardial infarction 2. dissecting aneurism or a perforated peptic ulcer of the esophagus. The case ended fatally without benefit of operation. The diagnostic clue in the case reported and in all previously reported cases was a peculiar murmur heard over the pericardium resembling the sound of water rushing through a narrow opening.

ALEXANDER ZABIN

STOMACH

LATE RESULTS OF VAGOTOMY COMBINED WITH GASTROJEJUNOSTOMY OR PYLOROPLASTY IN THE TREATMENT OF DUODENAL ULCERATION: J. A. Lloyd Davies. Brit. M. J. 5001:1086 (10 Nov.), 1956.

This review indicates that in a gratifying large proportion of cases complete vagotomy combined with an adequate gastric drainage operation is followed by a lasting cure of duodenal ulceration.

The finding of statistically similar figures for recurrent ulceration following vagotomy and gastrojejunostomy (5.6 per cent) and vagotomy and pyloroplasty (4.5 per cent) suggests that recurrence does not depend upon the completeness of vagal section. Support for this contention comes from the insulin-test-meal evidence of incomplete vagotomy found in all those cases of anastomotic or recurrent ulceration where the results of this investigation have been available. Nor has recurrent ulceration been found when vagotomy has been complete. Therefore it can only be presumed that the high recurrence rates reported in some series may be closely related to the incompleteness of vagal section. It is therefore of considerable importance that a surgical technic should be employed which is most likely to ensure complete division of the vagal nerves.

When the postoperative symptoms are considered the absence of severe post-

prandial "dumping" phenomena must be emphasized. Moreover, while the incidence of biliary regurgitation (14 per cent), diarrhea (19 per cent), flatulence (15 per cent), and hypoglycemic attacks (11 per cent) after vagotomy and gastrojejunostomy is not small, these symptoms were commonly minor and infrequent. Although direct comparison of symptoms with those occurring after partial gastrectomy is not easy, the figure of 92.4 per cent for clinically satisfactory results after vagotomy and gastrojejunostomy is similar to that generally quoted for Polya-type partial gastric resection. Furthermore, the numbers of patients completely symptom-free after either of these two operations correspond closely.

In some important respects, however, the results of vagotomy combined with a proper gastric drainage operation would appear to be better than those of Polya-type partial gastrectomy.

The evidence shows that vagotomy combined with gastrojejunostomy or pyloroplasty has a lower operative mortality rate than Polya partial gastrectomy.

Thus for the present the increased risk of recurrence would seem to preclude the general adoption of vagotomy and gastrojejunostomy as the elective procedure of choice in chronic duodenal ulceration.

When elective surgery is necessary in the treatment of duodenal ulceration, vagotomy and gastrojejunostomy seems to be indicated when it is essential that the postoperative calorie intake be high, as in patients who perform heavy physical work or who have pulmonary tuberculosis. Moreover, the satisfactory results obtained in women would favor its adoption in females in preference to subtotal gastric resection, in view of the disappointing clinical results which this latter operation often gives in this sex. Finally, the lower mortality rate also supports the use of vagotomy and gastrojejunostomy in old or poor risk patients.

JACOB A. RIESE

PEPTIC ULCER: Moses Behrend. J. Internat. Coll. Surgeons 26:401 (Oct.), 1956.

There is still much controversy as to treatment of peptic ulcer. In the opinion of the author too much time is wasted by medical management of ulcers, which may lead to perforation, hemorrhage and obstruction. As a good many ulcers may produce those complications, peptic ulcer must, therefore, be *per se* regarded as a surgical disease.

Hemorrhage from the intestinal tract—after due replacement of blood—especially a hemorrhage of massive and/or repeat nature should be subjected to early surgery.

Perforated ulcer may be treated by simple closure, subtotal resection and/or by medical management.

The technical aspects and the advantages of different surgical methods are discussed. The author states, that he has never performed vagotomy and posterior gastroenterostomy.

H. J. JOSEPH

CLINICAL APPLICATION OF GASTRIC CYTOLOGY: Robert E. Crozier, Margaret Middleton and John R. Ross. New England J. Med. 255:1128 (13 Dec.), 1956.

Cytology of the stomach is a new adjunct in making the diagnosis of a gastric lesion. In spite of its infancy and its still being subject to further improvement, its considerable value has already been proven.

The authors' method is as follows: after due preparation vigorous gastric lavage with saline solution is carried out. The Ewald evacuator tube was found best both for lavage and recovery of a specimen. Special emphasis is placed on the necessity of immediate processing of the specimen. The method is described in detail.

Gastric cytology may prove to be very useful in differentiating between benign and malignant lesions. The authors' accuracy was over 90 per cent.

On the other hand surgery could be avoided, if both routine examination, i.e. x-ray and gastroscopy, as well as cytology point to a benign lesion.

It is too early to judge the possibilities of this new procedure. Its greatest possible future value may be to provide a comparatively easy screening test in order to detect early gastric malignancy.

H. J. JOSEPH

INTESTINES

IDIOPATHIC SEGMENTAL INFARCTION OF THE GREATER OMENTUM: Cornelius J. Shea, Frank A. Pomer and John W. Spellman. New England J. Med. 254:263 (9 Feb.), 1956.

Idiopathic segmental infarction of the omentum, while a comparatively rare condition, should be considered in differential diagnosis with acute appendicitis or acute cholecystitis, as it, depending upon location can simulate either one.

Of the 43 cases reported in literature, all but four were preoperatively labeled as one or the other of these two abdominal emergencies. None were diagnosed as segmental infarction.

Many theories have been advanced to explain these infarctions, but common etiologic factors seem to be lacking and more experience with this condition will be necessary before adequate criteria for diagnosis can be established, but it should be considered in all acute abdominal conditions that do not show clear diagnostic symptoms.

Treatment consists of complete removal of the entire area of infarction to prevent complications of gangrene and adhesions.

J. EDWARD BROWN

PNEUMATOSIS COLI: Richard H. Marshak and Joan Eliasoph. Am. J. Digest. Dis. 1:99-107 (March), 1956.

Pneumatosis coli is a rare disease manifested by intramural collections of gas in the colon and its peritoneal attachments. *Pneumatosis intestinalis* is the more general term applied to the same condition involving any portion of the intestinal tract. As of 1952, the world literature contained 213 reported cases of *pneumatosis intestinalis* in 10 per cent of which the colon was affected. The authors present four new case reports in which the disease involved the left side of the colon only. On the basis of these cases the possible mechanism of causation is discussed and four pages full of excellent x-ray pictures are added.

WALTER CANE

CONSIDERATIONS ON TWO CASES OF PRIMARY EPITHELIOMA OF THE SMALL INTESTINE: J. Meillere. Semaine des Hopitaux 32:249-253 (April), 1956.

The author draws the attention to the clinical syndrome realized by gradually extending stenosis of the small intestine with stasis of its distal portion. In two cases he reports on primary collar-like epithelioma of the small intestine.

Both operated cases showed cylindrical glandular epithelioma with string-stricture of the small intestine and discreet tumoral reaction. The above situated ansa was distended, with thickened paries, filled with grumous, greenish, liquidless mass.

These syndromes, the one chronic with daily crisis, the other with acute irrevertible obstruction, were the "pure" clinical expression of the stasis of the ileum. This stasis of the ileum by progressive stenosis of the small intestine is remarkable by the characteristics of the vomiting, real vomiting by overflowing of substances accumulated above the stricture and by the surprising tolerance: all these characteristics are in relation with the classical syndrome of gastric stasis by stenosis of the pylorus.

ON BEHALF OF THE SURGICAL TREATMENT OF SIGMOIDITIS: Pierre Bertrand, Jacques Francillon et Jean-Paul DeVaux La Semaine des Hopitaux 32:327-334 (May), 1956.

Complications of this disorder are not seldom: occlusions, perforations, abscesses or fistulas and even an association with carcinoma should always be kept in mind.

The surgical forms are about 15 per cent of the whole.

Palliative methods, such as drainage and derivation, are not sufficient to obtain a real cure, but have the advantage of helping the patient to overcome a difficult situation.

The conservative methods (diverticulectomy or intussusception of a diverticle, su-

ture of a perforation or exenteropexis) have the disadvantage of a very limited action on a disease which has diffuse character.

For this reason, the choice should in principle prefer radical methods.

One may be obliged to perform emergency surgery, in the cases of complications.

AMEBIASIS: A REVIEW: I. PATHOGENESIS, PATHOLOGY AND CLINICAL MANIFESTATIONS. Harry Seneca. Am. J. Digest. Dis. 1:250-260 (June), 1956.

The subject is presented in a comprehensive and textbook like manner and can be highly recommended as a refresher course. Here are a few data of particular interest. The number of cysts voided per day varies from 330,000 to 45 million and occurs in cycles or crops. Apparently there is no difference in the virulence of the small and large ameba, and there is evidence that the small race may transform into the large variety. Children below 5 are rarely infected, and the highest rate of incidence is among persons 26 to 30 years of age. Hepatic amebiasis shows a ratio of 16.4 males to 1 female.

WALTER CANE

AMEBIASIS: A REVIEW: II. LABORATORY DIAGNOSIS, DIFFERENTIAL DIAGNOSIS, AND THERAPY. Harry Seneca. Am. J. Digest. Dis. 1:310-322 (July), 1956.

Valuable and detailed directions are given for collection and handling of stool specimens, of possible errors on microscopic examination, on the culture methods as well as those used for animal inoculation and for performing the complement fixation test. Important hints can be found as to possible pitfalls on sigmoidoscopic and x-ray interpretation. Differential diagnostic considerations are given their proper emphasis. The chapter on therapy starts with the following statement. "An ideal amebicide is a drug which is active *in vitro* and *in vivo* against the cysts and trophozoites of *E. histolytica*, is nontoxic, concentrates at the site of the pathology (colon and/or liver), and is reasonably cheap. As of the writing of this paper, no such drug fulfills all these criteria."

WALTER CANE

EPIDEMIC DIARRHEA OF THE NEWBORN CAUSED BY E. COLI SUBGROUP: H. Morris and R. A. Burger. J. Indiana State M. A. 49:1059 (Sept.), 1956.

The authors describe an epidemic of infectious diarrhea with involvement of 21 patients and 7 deaths occurring in the nursery of newborns. The etiologic organisms were *E. coli* strains 0127B8 and 0126.

The subgroups of *E. coli* were found to be sensitive to neomycin and all ill infants and new suspects were treated with this antibiotic. Every patient was maintained on neomycin until discharge. Prompt segregation of every patient with diarrhea was considered of primary importance in aborting the epidemic.

It is dangerous to be unaware that *E. coli* can be pathogenic in a nursery. These pathogenic strains should be considered as an etiologic agent of epidemic diarrhea of the newborn in addition to the familiar pathogens of the salmonella or shigella groups as well as virus agents.

JOSEPH E. WALTHER

DIOCTYL SODIUM SULFOSUCCINATE (DOXINATE) IN CHRONIC FUNCTIONAL CONSTIPATION: Marion Friedman. Am. Pract. & Digest. Treat. 7:1588 (Oct.). 1956.

The author reports a new type approach to the age-old problem of constipation using a material which softens the stool by lowering the surface tension and makes a more homogenous stool which is easily passed by the patient. He had good success with this material, but found it necessary to combine it with laxation in certain cases of atonic constipation. There were no bad side-effects noted.

ABE ALPER

THE CATASTROPHIC COMPLICATIONS OF ULCERATIVE COLITIS: CANCER, PERFORATION AND MASSIVE BLEEDING: Robert T. Tidrick and Robert C. Hickey. J. Iowa State M. Soc. 46:485-492 (Sept.), 1956.

Cancer, perforation and massive bleeding are considered as the three most prevalent catastrophic complications of ulcerative colitis. These authors have presented illustrative charts and photographs of specimens demonstrating this relationship and indicating time intervals and contributory relationships.

Intestinal perforation and massive bleeding as complications of acute ulcerative colitis or of violent exacerbations of the disease may be furthered by administration of adrenocorticotrophin (ACTH) or cortisone. The indications and difficulties incident to surgical therapy as a part of the emergency treatment in patients with perforation and hemorrhage are noted.

GLENN S. ROST

LIVER AND BILIARY TRACT

SURGERY OF THE BILIARY TRACT: (CONCLUDED) Richard B. Cattell and Kenneth W. Warren. New England J. Med. 255:761 (18 Oct.), 1956.

Stenosis of the sphincter of Oddi as a contributor to biliary tract symptoms is a concept that is gaining in importance even in those cases without common duct stones or previous biliary tract surgery. The need for evaluating the patency and calibre of the sphincter of Oddi in every common duct exploration is well illustrated in the series of 198 cases who had dilatation at the time of choledochostomy with no recurrence or reformation of stones, and the 10 per cent recurrence or reformation rate in the control series of 230 cases without dilatation at the time of choledochostomy. In 100 cases of stenosis of the sphincter of Oddi, Cattell, Colcock and Pollack achieved excellent results in 81 cases, and good results in 9 and poor results in 8 cases by transduodenal sphincterotomy with implantation of a long arm T-tube in 72 cases and simple dilatation by the Baki sound in 26 cases. These cases all presented a right upper quadrant syndrome of pain and 46 had a history of jaundice. Eighty-one had previous cholecystectomy without relief of original symptoms. Forty of these cases had choledochostomy with the cholecystectomy. Diagnosis was simplified by intravenous cholangiography. Dilatation over 15 mm. always meant obstruction, and if less than 15 mm. in diameter, persistence of density of visualization at 120 minutes was indicative of obstruction. Operative diagnosis of benign organic obstruction is made if a 3 mm. Baki dilator cannot be passed through the sphincter.

Choledochal cysts usually found in children are characterized by a clinical syndrome of a mass in the right upper quadrant associated with abdominal pain followed by jaundice and frequently by chills and fever. Treatment of choice is anastomosis of cyst to jejunum.

In wounds of the liver early surgery with careful debridement and intensive early antibiotic treatment is advocated.

"Operative cholangiography need" remains a controversial subject. The authors do not see the need if every indication for the exploration of the common duct is observed and the sphincter dilated with each choledochostomy and sphincterotomy is performed if the sphincter does not permit passage of a Baki dilator of sufficient size.

Postoperative stricture of the common duct is the most serious benign acquired disease of the biliary tract. Eighty per cent followed cholecystectomy performed in retrograde manner. The important point in treatment is the avoidance of strictures. In cases where anomalies exist or there is failure to visualize all structures clearly, a cholecystostomy and choledochostomy should be done instead of a cholecystectomy. In repairs an end-to-end anastomosis of the bile ducts should be done whenever possible. With failure to achieve this, anastomosis with the duodenum or jejunum should be done. The success of this procedure will depend on the avoidance of any obstruction at the anastomosis which in turn depends upon a healthy portion of proximal hepatic duct. Ascending infection does not occur with an adequate opening at the anastomosis.

JULES D. GORDON

BOOK REVIEWS FOR GASTROENTEROLOGISTS

THE IMPORTANCE OF OVERWEIGHT: Hilde Bruch, M.D. 438 pages. W. W. Norton Co., Inc., New York, N. Y., 1957. Price $5.95.

Here is a book which discusses overweight from the psychiatric standpoint. It is written by a physician who is a psychoanalyst and psychiatrist. Family background, heredity, diet and weight control are evaluated. Treatment and helpful suggestions throughout the volume should aid in prevention and reduction of overweight children and adults.

Quotations from world literature dealing with psychiatry and psychoanalysis, with a statistical analysis, extensive bibliography and index, add to the value of the book.

TEMAS DE GASTROENTEROLOGIA: Marcos Meeroff M.D.; Chief of the Service of Gastroenterology at the Hospital Lanus, Former Chief of Clinic and General Practice of the IV Catedra of Clinical Medicine of the Faculty of Medical Science of Buenos Aires, Arg. 755 pages, illustrated. Editorial Stilcograf, Buenos Aires, Arg., 1956.

The volume is divided into 28 chapters and after the introduction, the author begins his treatise with diverticula of the esophagus, continuing with the various organs of digestion. It is a well written and balanced book, with an adequate bibliography at the end of each chapter.

The author, Dr. Meeroff, is to be commended for the great amount of original work which is found between the covers of this beautifully printed and bound monograph.

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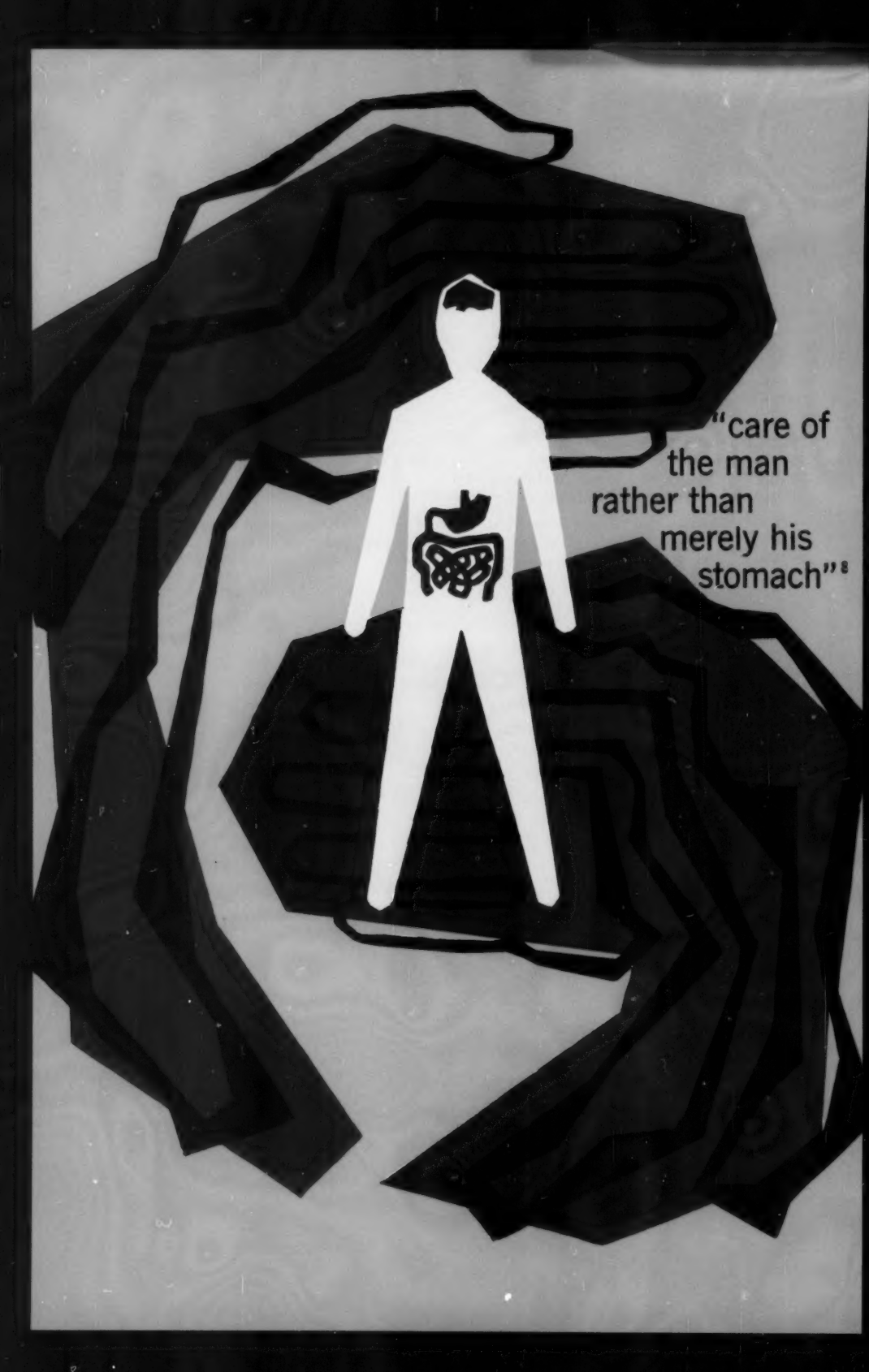
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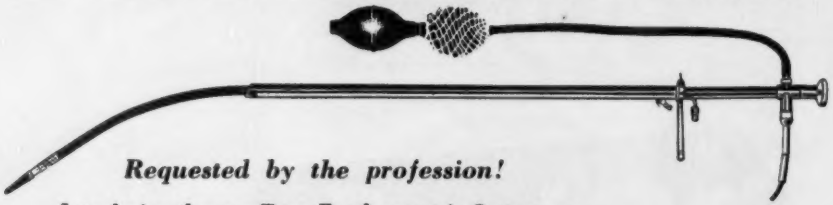

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4. Longer than the Standard Gastroscopes to permit full advantage of the flexible portion to be felt after it has been passed through the Esophagoscope.
5. Simplifies combination Gastroscopy and Esophagoscopy!
6. Instruments can be used individually or combined!
   One introduction — Two examinations!
7. Patient's discomfort reduced! Doctor's diagnostic areas increased!

For more information, **prices and descriptive folder #89**

Write the manufacturer

EDER INSTRUMENT COMPANY **2293 N. Clybourn Avenue**

Chicago 14, Illinois

NEW AMBULATORY TREATMENT

hastens healing of

Gastric and Duodenal Ulcers

Roentgenological healing of ulcer in 81% cases, relief of pain without analgesics in 92%, weight gains averaging 7.9 lbs. in 93%. Occult blood disappears from stools. No side effects, no after effects, no acid rebound.

This new therapy introduced from Holland (Pharmaceutische Fabriek Roter) is now available in the United States as Romach tablets, which contain finely particulated bismuth subnitrate (Romach process) combined with standard antacids.

Romach forms a protective coating of the ulcer bed, quickly relieving pain and also promoting rapid roentgenological healing.

Average dose, 2 tablets t.i.d., p.c. Available in boxes of 60, 150 and 660.

ROMACH

Write for Professional sample and literature.

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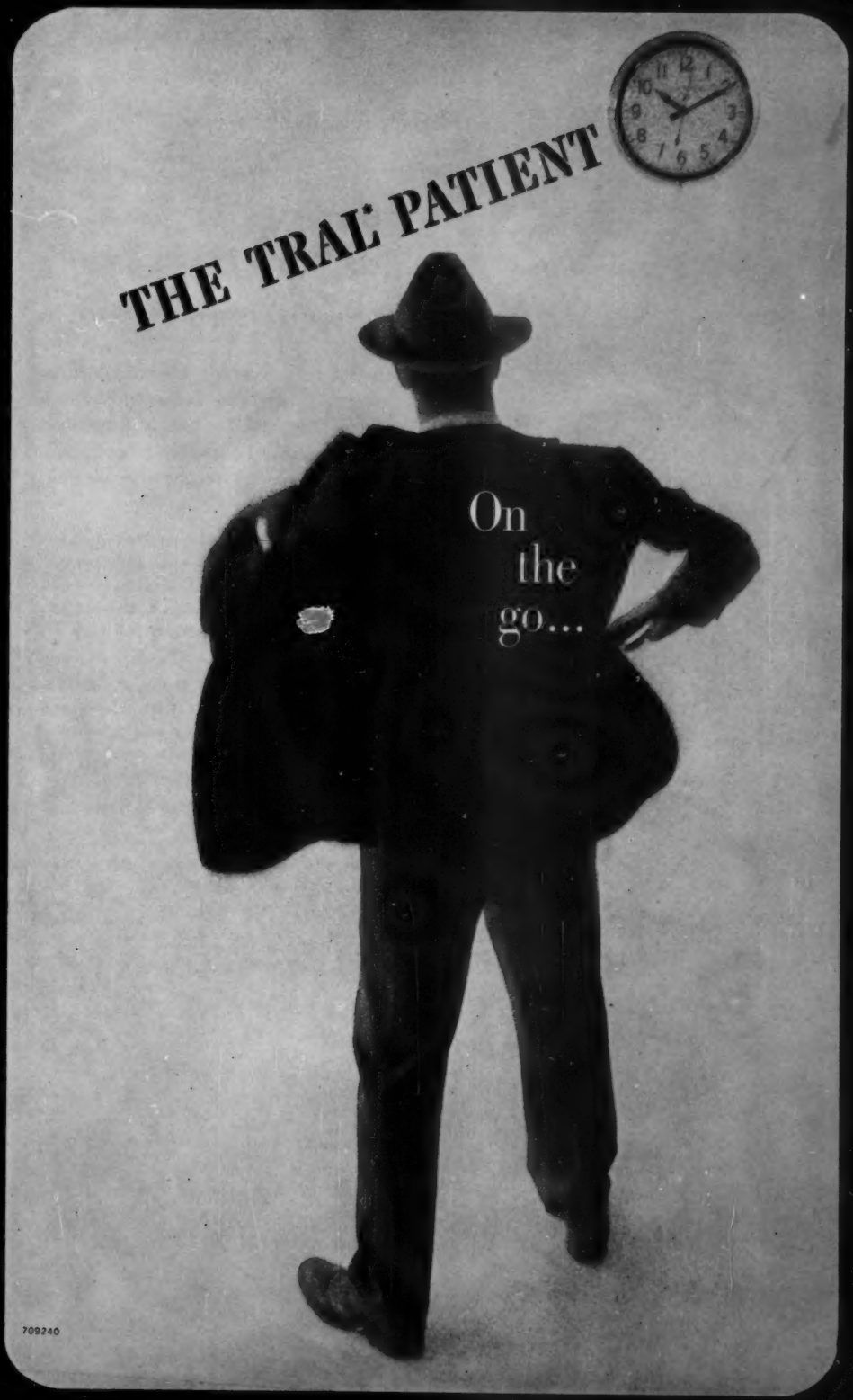
2268 First Ave., New York 35, N. Y

Please send me without obligation professional sample, and literature on Romach tablets.

..... M.D.

..... Street

City ..... Zone ..... State .....

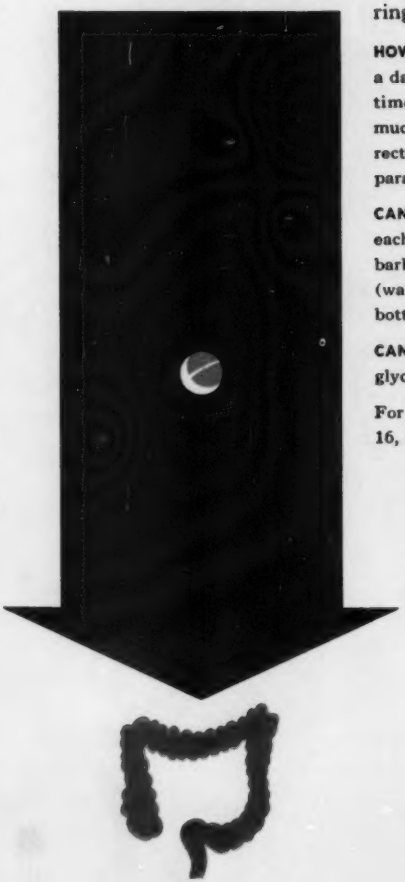

THE TRAL PATIENT
On
the
go...
709240

effective, selective therapy

Cantil
for the colon

for functional and organic disorders

CANTIL relieves pain, cramps, bloating...curbs diarrhea...restores normal tone and motility. Selective action focused on the colon avoids widespread interference with normal autonomic function... minimizes urinary retention, mouth dryness, blurring of vision.



HOW CANTIL IS PRESCRIBED One or two tablets three times a day preferably with meals, and one or two tablets at bedtime for patients with ulcerative colitis, irritable colon, mucous colitis, spastic colitis, diverticulitis, diverticulosis, rectospasm, diarrhea following G.I. surgery, bacillary and parasitic disorders.

CANTIL—TWO FORMS CANTIL (plain)—25 mg. of CANTIL in each scored tablet—bottles of 100. CANTIL with Phenobarbital—25 mg. of CANTIL and 16 mg. of phenobarbital (warning: may be habit forming) in each scored tablet—bottles of 100.

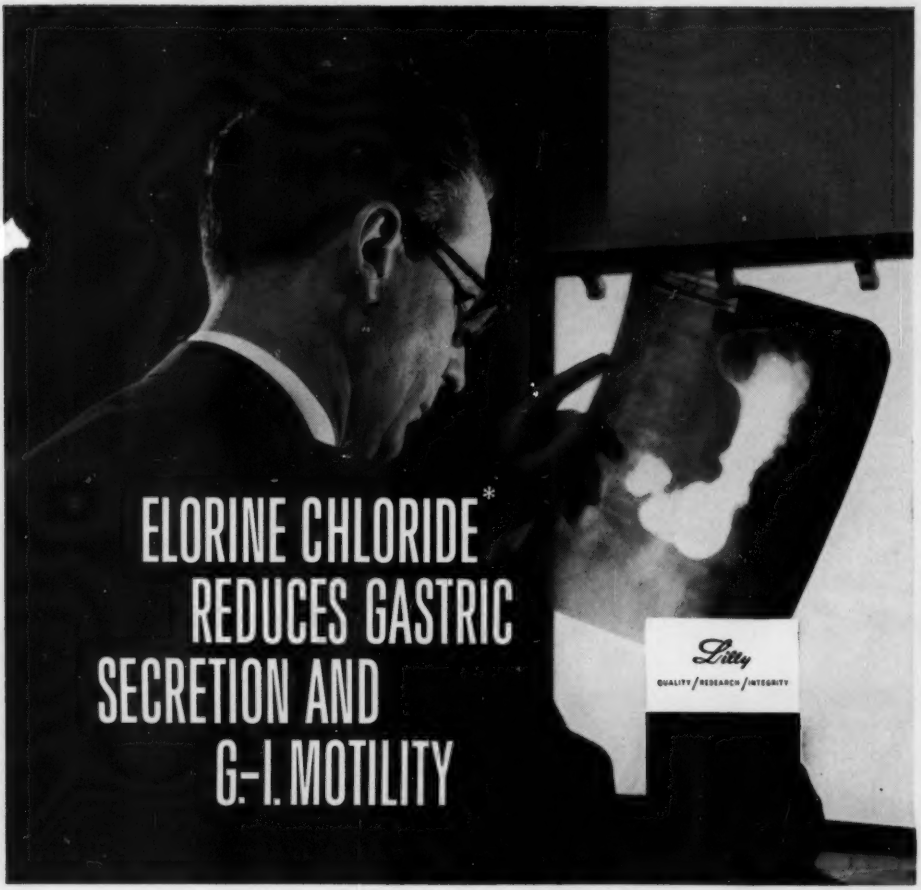
CANTIL is the *only* brand of N-methyl-3-piperidyl-diphenylglycolate methobromide.

For more detailed information, request Brochure No. NDA 16, Lakeside Laboratories, Milwaukee 1, Wisconsin.

LAKESIDE

14487

THE TRAL PATIENT
on
the
mend...
708249



Especially valuable in the management of peptic ulcer patients

The selective anticholinergic action of 'Elorine Chloride' has been shown to produce a "pronounced and significant" decrease in mean gastric volume, free and total acid, and pepsin output.[1] It also effectively reduces hypermotility of the gastro-intestinal tract (except the esophagus). Other conditions in which 'Elorine Chloride' is valuable include functional digestive disorders, acute pancreatitis, diverticulitis, pylorospasm, and excessive sweating.

Dosage should be tailored to patient tolerance. In peptic ulcer, the average adult dose ranges from 100 to 250 mg. three or four times daily. 'Elorine Chloride' is available in pulvules of 50 and 100 mg.

*'Elorine Chloride' (Tricyclamol Chloride, Lilly)

1. Sun, D. C. H., and Shay, H.: A.M.A. Arch. Int. Med., *97*:442, 1956.

ELI LILLY AND COMPANY · INDIANAPOLIS 6, INDIANA, U.S.A.

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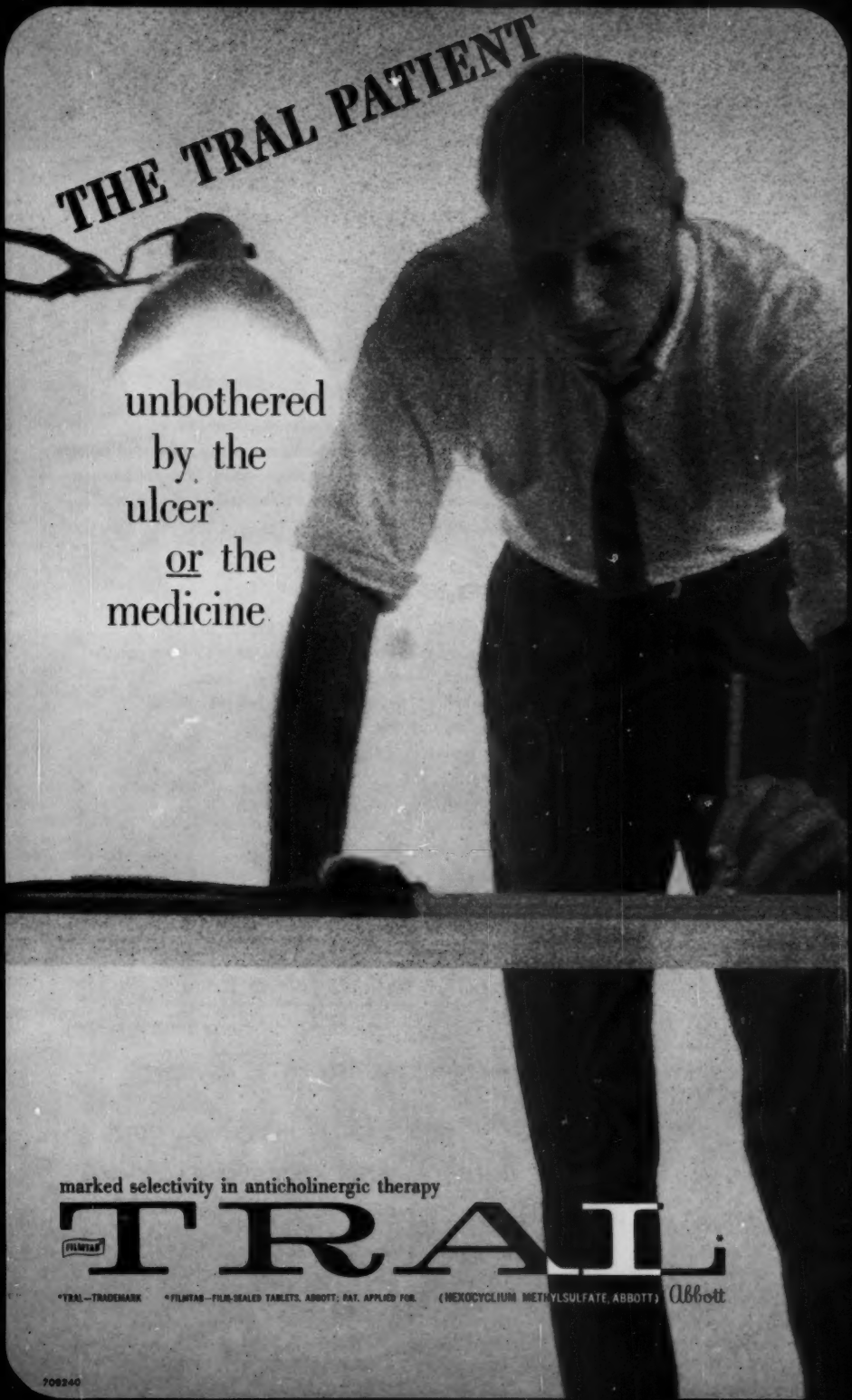
THE TRAL PATIENT
unbothered
by the
ulcer
or the
medicine
marked selectivity in anticholinergic therapy
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FILMTAB
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(HEXOCYCLIUM METHYLSULFATE, ABBOTT)
Abbott
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NEW PATHIB

combines **Meprobamate** *(400 mg.):*

Widely prescribed tranquilizer-muscle relaxant. Effectiveness in anxiety and tension states clinically demonstrated in millions of patients. Meprobamate acts only on the central nervous system. Does not increase gastric acid secretion. It has no known contraindications, can be used over long periods of time.[1,2,3]

with **Pathilon** *(25 mg.):*

An anticholinergic noted for its extremely low toxicity and high effectiveness in the treatment of G.I. tract disorders. In a comparative evaluation of currently employed anticholinergic drugs, PATHILON ranked high in clinical results, with few side effects, minimal complications, and few recurrences.[4]

Now...with **PATHIBAMATE**...*you can control disorders of the digestive tract and the "emotional overlay" so often associated with their origin and perpetuation...without fear of barbiturate loginess, hangover or addiction. Among the conditions which have shown dramatic response to* **PATHIBAMATE** *therapy:*

DUODENAL ULCER • GASTRIC ULCER • INTESTINAL COLIC
SPASTIC AND IRRITABLE COLON • ILEITIS • ESOPHAGEAL SPASM
ANXIETY NEUROSIS WITH G.I. SYMPTOMS • GASTRIC HYPERMOTILITY

AMATE*

Meprobamate with PATHILON® LEDERLE

Comments on PATHIBAMATE *from clinical investigators*

- "I find it easy to keep patients using the drug continuously and faithfully. I feel sure this is due to the desirable effect of the tranquilizing drug."[3]

- "The results in several people who were previously on belladonna-phenobarbital preparations are particularly interesting. Several people volunteered that they felt a great deal better on the present medication and noted less of the loginess associated with barbiturate administration."[6]

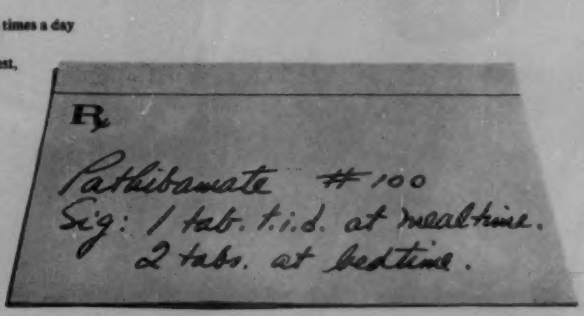
- PATHIBAMATE..."will favorably influence a majority of subjects suffering from various forms of gastrointestinal neurosis in which spasmodic manifestations and nervous tension are major clinical symptoms."[7]

- "In the patients with functional disturbances of the colon with a high emotional overlay, this has been to date a most effective drug."[5]

eferences: 1. Borrus, J. C.: *M. Clin. North America,* press, 1957. 2. Gillette, H. E.: *Internat. Rec. Med. & G. P. lin.* 169:453, 1956. 3. Pennington, V. M.: *J.A.M.A.,* press, 1957. 4. Cayer, D.: Prolonged Anticholinergic herapy of Duodenal Ulcer. Am. J. Dig. Dis. 1:301-309 uly) 1956. 5. McGlone, F. B.: Personal Communication to ederle Laboratories. 6. Texter, E. C., Jr.: Personal ommunication to Lederle Laboratories. 7. Bauer, H. G. d McGavack, T. H.: Personal Communication Lederle Laboratories.

upplied: Bottles of 100 and 1000

dministration and Dosage: 1 tablet three times a day mealtimes and 2 tablets at bedtime. Full formation on PATHIBAMATE available on request, see your local Lederle representative.



Lederle LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY, PEARL RIVER, NEW YORK

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Announcing . . . a new useful dosage form of Equanil

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- Especially coated, easy to swallow
- Tranquilizer-conscious patients will not recognize new yellow tablets
- Different from regular 400-mg. and 200-mg. tablets
- Same indications, same dosage as original EQUANIL

NOW YOU HAVE A CHOICE OF 3 EQUANIL TABLETS

WYSEALS EQUANIL, 400 mg.
Yellow tablets, bottles of 50.

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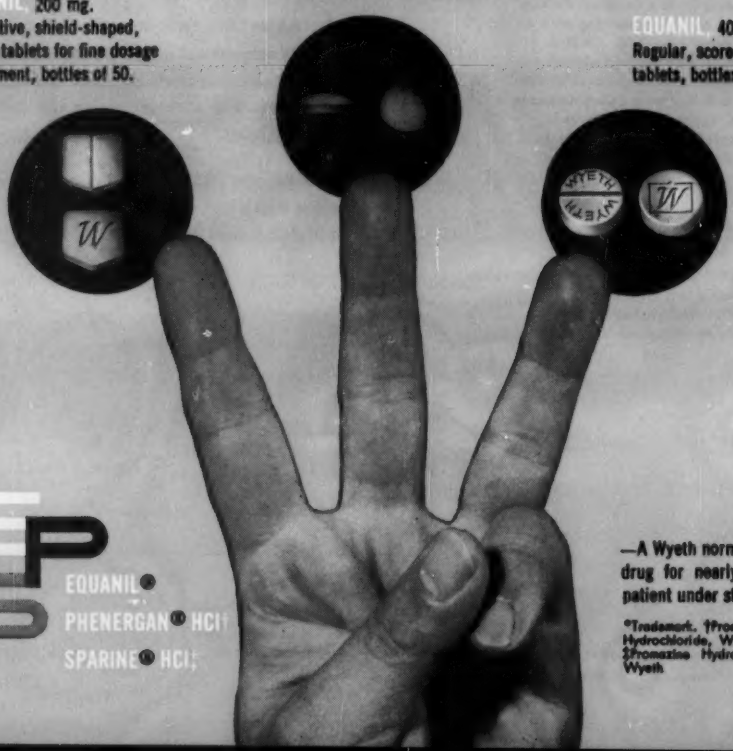
Distinctive, shield-shaped, scored tablets for fine dosage adjustment, bottles of 50.

EQUANIL, 400 mg.
Regular, scored, white tablets, bottles of 50.



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EQUANIL®
PHENERGAN® HCl†
SPARINE® HCl‡

—A Wyeth normotropic drug for nearly every patient under stress

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don't forget...
– to correct abnormal bowel function (either constipation or non-specific diarrhea)
– eliminate the high roughage foods containing irritating bulk (lignin and cellulose)
– and replace them with
KONSYL
(the bowel normalizer of choice)

Konsyl supplies a non-irritating bulk consisting entirely of hemicelluloses derived from blond psyllium. The smooth-bulk of Konsyl disperses with the intestinal contents to create a soft-formed, easily passed stool. Konsyl assures the resumption of a normal peristaltic pattern and contains no sugar or other diluents.

Made by **BURTON, PARSONS & COMPANY** *Since 1932*

Originators of Fine Hydrophilic Colloids

WASHINGTON 9, D. C.

when he smokes too much . . .

Whenever indigestion results from habitual overdoing in any form (excess of cigarettes or alcohol, dietary indiscretion, nervous tension), symptoms can be quickly alleviated night and day with Gelusil and the new formulation Gelusil-Lac.

To avoid daytime distress: Gelusil provides the sustained action of magnesium trisilicate and specially prepared aluminum hydroxide gel to restore and maintain gastric pH within normal range. Because it does not overneutralize or alkalize, Gelusil avoids the twin dangers of acid rebound and systemic alkalosis.

To prevent middle-of-the-night attacks: In Gelusil-Lac, the proven antacid action of Gelusil is combined with sustained buffering effect of specially prepared high protein (low fat) milk solids to prevent gastric pain at night.

Nonconstipating: The specially prepared aluminum hydroxide component in Gelusil has a low order of chemical activity. Thus formation of astringent – and constipating – aluminum chloride is minimal.

Dosage: 2 Gelusil tablets or 2 teaspoonfuls Gelusil liquid two hours after eating or when symptoms are pronounced. Each tablet or teaspoonful provides: 7½ gr. magnesium trisilicate and 4 gr. aluminum hydroxide gel. Gelusil-Lac: At bedtime, one heaping tablespoonful stirred rapidly into one-half glass (4 fl. oz.) of cool water. (Provides equivalent of 4 Gelusil tablets.)

Gelusil®/Gelusil-Lac

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